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UNITED STATES PATENT APPLICATION

FOR

A METHOD OF PROVIDING A STEROID-SPARING BENEFIT WITH A CYCLOOXYGENASE-2 INHIBITOR AND COMPOSITIONS THEREWITH

OF

KAREN SEIBERT
(US citizen)
147 Marine Lane
St. Louis, MO 63146

ASSIGNED TO:
PHARMACIA CORPORATION
700 CHESTERFIELD PARKWAY WEST
CHESTERFIELD, MO 63017-1732

A METHOD OF PROVIDING A STEROID-SPARING BENEFIT WITH A CYCLOOXYGENASE-2 INHIBITOR AND COMPOSITIONS THEREWITH

CROSS-REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

[0001] This application is related to and claims the priority benefit of U.S. Provisional Patent Application Serial No. 60/458,595 filed March 28, 2003, which is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

[0002] The present invention relates generally to the use of a cyclooxygenase-2 inhibitor to provide steroid-sparing benefits and, more particularly, to the use of a cyclooxygenase-2 inhibitor in combination with a corticosteroid to provide steroid-sparing benefits for the treatment of inflammatory disorders.

(2) Description of the Related Art:

[0003] Currently, the front-line therapy of choice for a variety of immune and inflammatory disorders are corticosteroids, which have the ability to suppress immunologic and inflammatory responses. *See* Barnes, *et al., J. Allergy Clin. Immunol.*, *101*:S427-33. Corticosteroids are routinely used in the treatment of inflammation arising from asthma, chronic obstructive pulmonary disease, (COPD), autoimmune diseases and various dermatological disorders. *See e.g.,* Sterry, *et al., W. Arch. Dermatol. Res. 284*:S27-S29 (1992).

[0004] Corticosteroids exert their effects by binding to the steroid-binding domain of glucocorticoid receptors found throughout the body. *See* Barnes, P., *et al., Am. J. Respir. Crit. Care Med.*, *157*:S1-S53 (1998). Corticosteroid binding activates glucocorticoid receptors, causing them to translocate to the nucleus and bind to glucocorticoid response elements (GREs) in the promoters of steroid-responsive genes. Once glucocorticoid receptors bind to their associated GREs, their physical binding results in the downregulation of pro-inflammatory genes (*e.g.* cytokines and

cyclooxygenase-2), while anti-inflammatory genes become upregulated (*e.g.* β_2-adrenoreceptor). *Id.*

[0005] Administration of a corticosteroid to a subject suffering from such inflammatory disorders as asthma and COPD limits inflammatory cell activities such as mast cell degranulation, histamine release, cytokine production, bronchoconstriction, and attraction of inflammatory cells to the site of an allergic reaction. Representative inflammatory cell-types include eosinophils, $CD4^+$ T lymphocytes, macrophages, neutrophils, dendritic cells, mast cells, and structural cells. *See* Bundschuh, D., *et al.*, *Pharm. Exper. Therap., 297*(1):280-290 (2001). These inflammatory cells release a plethora of mediators, including histamine and the products of arachidonic acid metabolism, such as leukotrienes, prostaglandins, cytokines, interleukins IL-1 to IL-12, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) and proteases, all ultimately leading to the harmful inflammatory symptoms and the histopathology of asthma. Therefore, corticosteroids treat asthma and COPD by decreasing inflammation and swelling in the airways and lessening airway hyperreactivity to irritants and allergens.

[0006] In some instances, corticosteroid administration can result in unintended and unwanted side effects. For inhaled corticosteroids, those side effects can include fungal infections of the mouth and throat (thrush), hoarseness, cough, and delayed growth. For more severe or chronic forms of asthma and COPD, orally ingested corticosteroids are prescribed as short-term burst therapies to treat acute severe episodes or as routine maintenance therapies. Although there are several different oral corticosteroids available, prednisone is the most commonly prescribed orally ingested corticosteroid. Orally prescribed steroids are known to cause severe side effects, especially with higher doses and during the course of long-term therapies.

[0007] For example, high doses of oral corticosteroids can cause suppression of growth, suppression of the pituitary and adrenal glands, osteoporosis, loss of blood supply to the bones, obesity, cataracts, high

blood pressure, weight gain, increase in body hair and acne, diabetes, muscle weakness, stomach irritations, emotional disturbances, and several other adverse effects.

[0008] Other unintended effects may develop with long-term inhaled and oral corticosteroid therapies, such as steroid resistance and steroid rebound effects. Resistance to corticosteroids may develop over time to maintenance therapies, thus requiring increasingly higher dosing and a corresponding increase in side effects. Likewise, certain inflammatory or immunological diseases exhibit refractoriness to steroid treatment (disease resistance). *See* U.S. Patent No. 6,054,487 to Sekut, *et al.* It has also been noted that sudden cessation of corticosteroid therapy can give rise to an apparent worsening of the original inflammatory symptoms (steroid-rebound effect).

[0009] Therefore, oral corticosteroid therapy requires careful monitoring by the prescribing physician, and continual efforts to wean the subject from the corticosteroids as soon as possible. Because many of the side effects from corticosteroid usage appear to be dose-dependent, clinicians have continued to search for alternative therapies that reduce the level of corticosteroids required for a particular benefit level (hereinafter referred to as steroid-sparing benefits).

[00010] Typical of the development of inflammatory symptoms is upregulation of the enzyme, cyclooxygenase-2 (Cox-2). Cox-2 is an enzyme that is produced by an inducible gene, which is responsible for the biosynthesis of prostaglandins in inflammatory cells. Inflammation causes the induction of Cox-2, leading to the release of prostanoids (prostaglandin E2), which sensitize peripheral nociceptor terminals and produce localized inflammation and oedema. *See e.g.* Samad, T. A. *et al., Nature* *410*(6827):471-5 (2001).

[00011] Historically, physicians have treated inflammation-related disorders with a regimen of nonsteroidal anti-inflammatory drugs (NSAIDs), such as, for example, aspirin and ibuprofen. Undesirably, however, some NSAIDs are known to cause gastrointestinal (GI) bleeding

or ulcers in subjects undergoing consistent long term regimens of NSAID therapy.

[00012] A reduction of unwanted side effects of common NSAIDs was made possible by the discovery that two cyclooxygenases are involved in the transformation of arachidonic acid as the first step in the prostaglandin synthesis pathway. These enzymes exist in two forms and have been termed cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2). *See* Needleman, P., *et al., J. Rheumatol. 24, Suppl.49*:6-8 (1997) and Fu, J., *et al., J. Biol. Chem. 265(28)*:16737-40 (1990).

[00013] Cox-1 is a constitutive enzyme responsible for the biosynthesis of prostaglandins in the gastric mucosa and in the kidney. Many common NSAIDs are now known to be inhibitors of both Cox-1 and Cox-2. Accordingly, when administered in sufficiently high levels, these NSAIDs not only alleviate the inflammatory consequences of Cox-2 activity, but also inhibit the beneficial gastric maintenance activities of Cox-1.

[00014] Research into the area of arachidonic acid metabolism has resulted in the discovery of compounds that inhibit the Cox-2 enzyme to a greater extent than the activity of Cox-1. The Cox-2 selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of Cox-1. Thus, Cox-2 selective inhibitors have shown great promise for use in therapies -- especially in therapies that require maintenance administration, such as for pain and inflammation control.

[00015] From the foregoing, it can be seen that a need exists for improved methods and therapeutic compositions that enable the use of lower effective dosage of corticosteroids -- in other words, which provide steroid-sparing benefits. It would also be useful to provide an improved method for reducing the unwanted side effects associated with corticosteroids. Likewise, methods that reduce the chances for developing corticosteroid resistance and also ameliorate the effects of steroid rebound would also be highly desirable. Finally, methods that improve the efficacy

of treating a disorder that is considered corticosteroid-resistant would be desirable.

SUMMARY OF THE INVENTION

[00016] Briefly, therefore, the present invention is directed to a novel method of providing a steroid-sparing benefit to a subject that is in need of, or that is presently receiving, a corticosteroid, the method comprising administering to the subject a Cox-2 inhibitor in combination with a corticosteroid.

[00017] The present invention is also directed to a novel method of preventing or treating a corticosteroid-responsive disease or disorder in a subject comprising administering to the subject a Cox-2 inhibitor in combination with a corticosteroid.

[00018] The present invention is also directed to a novel method for the treatment or prevention of pain, inflammation or an inflammation-related disorder in a subject comprising administering to the subject a Cox-2 inhibitor and a corticosteroid.

[00019] The present invention is also directed to a novel therapeutic composition comprising a Cox-2 inhibitor and a corticosteroid.

[00020] The present invention is also directed to a novel pharmaceutical composition comprising a Cox-2 inhibitor, a corticosteroid, and a pharmaceutically acceptable carrier.

[00021] The present invention is also directed to a novel kit comprising one dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a corticosteroid.

[00022] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of methods and therapeutic compositions that enable the use of lower effective dosage of corticosteroids -- in other words, which provide steroid-sparing benefits; and also the provision of an improved method for reducing the unwanted side effects associated with corticosteroids; and also the provision of methods that reduce the chances for developing corticosteroid resistance and also ameliorate the effects of steroid rebound would also be highly

desirable; and also the provision of methods that improve the efficacy of treating a disorder that is considered corticosteroid-resistant would be desirable.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00023] In accordance with the present invention it has been discovered that a steroid-sparing benefit can be provided to a subject that is in need of, or that is presently receiving, a corticosteroid, by administering to the subject a Cox-2 inhibitor in combination with a corticosteroid. This method can be used for preventing or treating a corticosteroid-responsive disease or disorder, such as asthma, in a subject that is in need of the prevention or treatment of this type of disease or disorder. It has been found that the method is particularly effective when the Cox-2 inhibitor is selective for the inhibition of the Cox-2 enzyme, and, celecoxib, in particular, has been found to be a preferred Cox-2 inhibitor.

[00024] The administration of the combination of the Cox-2 inhibitor with a corticosteroid has been found to be unexpectedly superior to the use of a corticosteroid alone, because the presence of the Cox-2 inhibitor permits the use of a lower amount of the corticosteroid to obtain the same therapeutic benefit than when the corticosteroid is administered without the Cox-2 inhibitor.

[00025] The terms "corticosteroids" and "steroids," both used interchangeably herein, refer to all steroid medications that have or exhibit or can be expected to exhibit any capability of modulating the activity of glucocorticoid-responsive receptors, such as, for example, the glucocorticoid receptor. As used herein, the term "corticosteroid" is intended to encompass the glucocorticoid subcategory of corticosteroids, but not mineralocorticoids.

[00026] Both corticosteroids and Cox-2 inhibitors are known separately for treating inflammation, and it is known that corticosteroids are associated with potentially harmful side-effects and a steroid-rebound effect. However, it was unexpected that the administration of a Cox-2

inhibitor in combination with a corticosteroid would provide the steroid-sparing benefits that are obtained.

[00027] As used herein, the term "steroid-sparing benefit" refers to the capacity of a Cox-2 inhibitor, when administered with a corticosteroid to a subject in need of, or who is receiving, a corticosteroid medicament, to enhance the therapeutic benefits provided by a given amount of the corticosteroid. In other words, administering to a subject a corticosteroid and a Cox-2 inhibitor synergistically combines the effects of both treatments providing for treatment of the indicated disorder and sparing the amount of corticosteroid that normally would have been required without the synergistic addition of the Cox-2 inhibitor. A steroid-sparing benefit also includes the synergistic addition of a Cox-2 inhibitor that can help keep the disorder under control while corticosteroids are being tapered.

[00028] The combination therapy of a Cox-2 inhibitor and a corticosteroid is also useful for decreasing the required number of separate dosages, thus, potentially improving patient compliance. For example, in one embodiment, the combination therapy of the present invention is useful for reducing the dosing frequency of corticosteroids. Thus, administering the combination therapy of the present invention to a subject undergoing multiple dosings with a corticosteroid may reduce the required number of separate doses normally prescribed.

[00029] As used herein, the phrases "combination therapy", "co-administration", "administration with", or "co-therapy", when referring to use of a Cox-2 inhibitor and a corticosteroid, are intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner. The phrase "combination therapy" also can embrace the administration of the combination of therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies.

[00030] Substantially simultaneous administration can be accomplished, for example, by administering to the subject the Cox-2 inhibitor and corticosteroid together in one therapeutic dosage form, such as in a single capsule, tablet, or injection, or in multiple separate therapeutic dosage forms, such as in separate capsules, tablets, or injections.

[00031] Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, subcutaneous routes, intraarticular routes, and direct absorption through mucous membrane tissues. Each therapeutic agent can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the second therapeutic agent of the combination may be administered orally. Alternatively, for example, both therapeutic agents may be administered orally or both therapeutic agents may be administered by intravenous injection.

[00032] Sequential administration of such treatments encompasses both relatively short and relatively long periods between the administration of each of the compounds of the present method. However, for purposes of the present invention, the second compound is administered while the first compound is still having an efficacious effect on the subject. Thus, the present invention, in one embodiment, takes advantage of the fact that the simultaneous presence of the combination of a Cox-2 inhibitor and a corticosteroid in a subject has a greater efficacy than the administration of either one of the agents alone.

[00033] Preferably, the second compound is to be given to the subject within the therapeutic response time of the first compound to be administered.

[00034] As used herein, the terms "therapeutic response time" mean the duration of time after administration that a compound has a therapeutic effect within a subject's body.

[00035] For example, the present invention encompasses administration of a Cox-2 inhibitor to the subject and the later administration of a corticosteroid as long as the corticosteroid is administered to the subject while the Cox-2 inhibitor is still present in the subject at a level, which in combination with the level of the corticosteroid, is therapeutically effective, and vice versa.

[00036] The administration of lowered dosages of corticosteroids can, in one embodiment, provide a reduction in side effects corresponding to such agents. Lowered dosages of corticosteroids are beneficial where normal dosages often exhibit harmful side effects.

[00037] The phrases "reduced dosages", "lowered dosages", "low dose", or "low dose amount", in characterizing a therapeutically effective amount of the Cox-2 inhibitor and the corticosteroid in the combination therapy, defines a quantity of such agent, or a range of quantity of such agent, that is capable of reducing or avoiding one or more side effects of a monotherapy with the corticosteroid, while optionally reducing the discomfort from pain and/or inflammation.

[00038] For purposes of the present invention, the novel combination therapy comprising a Cox-2 inhibitor in combination with a corticosteroid is also useful for the purpose of preventing and/or treating pain or inflammation, and in preferred embodiments, inflammation-related disorders, in a subject.

[00039] In preferred embodiments, the subject is one that is in need of the prevention or treatment of pain or inflammation, and in preferred embodiments, an inflammation-related disorder.

[00040] Thus, the combination therapy of the present invention would be useful, for example, to reduce symptoms such as pain and inflammation, and in preferred embodiments, such symptoms as 1) pain; 2) swelling; 3) edema; 4) redness; 5) tissue damage; 6) fever; 7) cellular injury; and/or 8) relieving or reducing the side effects associated with the administration of anti-inflammatory agents. The combination therapy of

the present invention would also be useful to prevent the occurrence of such symptoms.

[00041] The novel combination of the present invention prevents and treats these pain and inflammation symptoms in a subject regardless of the underlying cause of the symptom being treated or prevented. However, in preferred embodiments, the novel combination prevents and treats such symptoms when their underlying cause is an inflammation-related disorder, and in further preferred embodiments, when their underlying cause is one of the inflammation-related disorders described herein. In still further preferred embodiments, the novel combination of the present invention is useful for the prevention and/or treatment of an inflammation-related disorder.

[00042] In preferred embodiments, the methods and compositions of the present invention are also useful to reduce the number of hospitalizations of subjects suffering from pain or inflammation, and in preferred embodiments, inflammation-related disorders, or to prevent or retard, in subjects, the development of complications associated with inflammation, which may eventually arise from having an inflammation-related disorder.

[00043] In one embodiment, the present invention encompasses a method for preventing a pain, inflammation or an inflammation-related disorder in a subject, the method comprising administering to the subject a Cox-2 inhibitor in combination with a corticosteroid.

[00044] As used herein, the terms "to prevent", "preventing", or "prevention" refer to any reduction, no matter how slight, of a subject's predisposition or risk for developing pain, inflammation or an inflammation-related disorder. For purposes of prevention, the subject is any subject, and preferably is a subject that is at risk for, or is predisposed to, developing pain, inflammation or an inflammation-related disorder. The term "prevention" includes either preventing the onset of clinically evident inflammation altogether or preventing the onset of preclinically evident inflammation in individuals at risk. Also intended to be encompassed by

this definition is the prevention of initiation for inflammatory cells or to arrest or reverse the progression of the inflammation cascade. This includes prophylactic treatment of those at risk of developing the inflammation.

[00045] As used herein, a subject that is "predisposed to developing pain, inflammation, or an inflammation-related disorder" or "at risk for developing pain, inflammation, or an inflammation-related disorder," both of which are used interchangeably herein, includes any subject with an increased chance for developing pain, inflammation, or an inflammation-related disorder. The subject may be at risk due to genetic predisposition, diet, age, exposure to pain or inflammation causing agents, and the like. The subject may also be at risk for re-developing inflammation during a relapse of such a disorder. The subject may also be at risk due to physiological factors such as anatomical and biochemical abnormalities and certain autoimmune diseases.

[00046] In another embodiment, the present invention encompasses a method for treating pain, inflammation and/or inflammation-related disorders in a subject, the method comprising administering to the subject a Cox-2 inhibitor in combination with a corticosteroid.

[00047] As used herein, the terms "treating", "treatment", "treated", or "to treat," mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to alter or slow the appearance of symptoms or symptom worsening. The term "treatment" includes alleviation or elimination of causation of pain and/or inflammation, and in preferred embodiments, pain and/or inflammation associated with, but not limited to, any of the inflammation-related disorders described herein.

[00048] In a preferred embodiment, a Cox-2 inhibitor is used to reduce the dosage of a corticosteroid needed for the treatment or prevention of an inflammatory disorder. In another preferred embodiment, the present invention is intended to reduce the dosages and/or side-effects of a subject that undergoing a corticosteroid therapy for any disorder that is related in any way to an inflammatory process. In preferred

embodiments, the methods and compositions of the present invention are used to reduce the dosages and/or side-effects of a corticosteroid therapy for pain or inflammation, or in preferred emobodiments, inflammation-related disorders, in a subject suffering from pain, inflammation, or an inflammation-related disorder.

[00049] Inhibitors of the Cox pathway in the metabolism of arachidonic acid that are used in the treatment, prevention or reduction of pain or inflammation may inhibit enzyme activity through a variety of mechanisms. By way of example, the Cox-2 inhibitors used in the methods described herein may block the enzyme activity directly by binding at the substrate site of the enzyme. In preferred embodiments, the use of a Cox-2 selective inhibitor is highly advantageous in that it minimizes the gastric side effects that can occur with non-selective non-steroidal anti-inflammatory drugs (NSAIDs), especially where prolonged treatment is expected.

[00050] The terms "cyclooxygenase-2 inhibitor", or "Cox-2 inhibitor", which can be used interchangeably herein, embrace compounds, which inhibit the Cox-2 enzyme regardless of the degree of inhibition of the Cox-1 enzyme, and include pharmaceutically acceptable salts of those compounds. Thus, for purposes of the present invention, a compound is considered a Cox-2 inhibitor irrespective of whether the compound inhibits the Cox-2 enzyme to an equal, greater, or lesser degree than the Cox-1 enzyme.

[00051] In one embodiment of the present invention, it is preferred that the Cox-2 inhibitor compound is a non-steroidal anti-inflammatory drug (NSAID). Therefore, preferred materials that can serve as the Cox-2 inhibitor of the present invention include non-steroidal anti-inflammatory drug compounds, a pharmaceutically acceptable salt thereof, mixed isomer, or a pure (-) or (+) optical isomeric form thereof.

[00052] Examples of NSAID compounds that are useful in the present invention include acemetacin, acetyl salicylic acid, alclofenac, alminoprofen, azapropazone, benorylate, benoxaprofen, bucloxic acid,

carprofen, choline magnesium trisalicylate, clidanac, clopinac, dapsone, diclofenac, diflunisal, droxicam, etodolac, fenoprofen, fenbufen, fenclofenec, fentiazac, floctafenine, flufenisal, flurbiprofen, (r)-flurbiprofen, (s)-flurbiprofen, furofenac, feprazone, flufenamic acid, fluprofen, ibufenac, ibuprofen, indometacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketorolac, miroprofen, piroxicam, meloxicam, mefenamic, mefenamic acid, meclofenamic acid, meclofen, nabumetone, naproxen, niflumic acid, oxaprozin, oxipinac, oxyphenbutazone, phenylbutazone, podophyllotoxin derivatives, proglumetacin, piprofen, pirprofen, prapoprofen, salicylic acid, salicylate, sudoxicam, suprofen, sulindac, tenoxicam, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, zidometacin, zomepirac, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, a 4-(nitrooxy)butyl ester, and mixtures thereof.

[00053] Further preferred NSAID compounds include ibuprofen, naproxen, sulindac, ketoporfen, fenoprofen, tiaprofenic acid, suprofen, etodolac, carprofen, ketrolac, piprofen, indoprofen, salicylic acid, flurbiprofen, and mixtures thereof.

[00054] In a preferred embodiment, the Cox-2 inhibitor is a Cox-2 selective inhibitor. The term "Cox-2 selective inhibitor" embraces compounds, which selectively inhibit the Cox-2 enzyme over the Cox-1 enzyme, and also include pharmaceutically acceptable salts and prodrugs of those compounds.

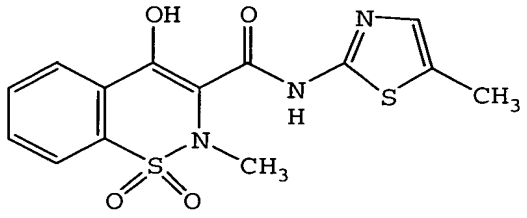
[00055] In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of Cox-1, divided by the IC_{50} value for inhibition of Cox-2 (Cox-1 IC_{50}/Cox-2 IC_{50}). A Cox-2 selective inhibitor is any inhibitor for which the ratio of Cox-1 IC_{50} to Cox-2 IC_{50} is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

[00056] As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of Cox activity. Preferred Cox-2 selective inhibitors of the present invention have a Cox-2 IC_{50} of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM.

[00057] Preferred Cox-2 selective inhibitors have a Cox-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

[00058] Also included within the scope of the present invention are compounds that act as prodrugs of Cox-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is sodium parecoxib. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598.

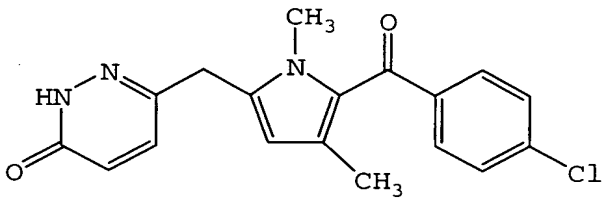
[00059] The Cox-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



B-1

[00060] In another embodiment of the invention the Cox-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.



B-2

[00061] The meaning of any substituent at any one occurrence in Formula I, or any other general chemical formula herein, is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

[00062] The term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The number of carbon atoms can also be expressed as "C_1-C_5", for example. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the, like. The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. Unless otherwise noted, such radicals preferably contain from 2 to about 6 carbon atoms, preferably from 2 to about 4 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropylenyl, buten-1yl, isobutenyl, penten-1yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like. The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such

radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups as described below. Examples of suitable alkynyl radicals include ethynyl, proynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

[00063] The term "oxo" means a single double-bonded oxygen.

[00064] The terms "hydrido", "-H", or "hydrogen", denote a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical, or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2 -) radical.

[00065] The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. Likewise, the term “halo”, when it is appended to alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heteroaryl, and the like, includes radicals having mono-, di-, or tri-, halo substitution on one or more of the atoms of the radical.

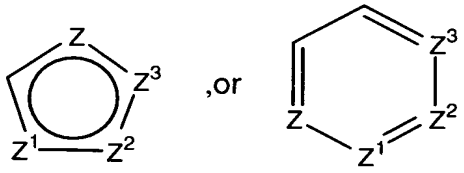
[00066] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals.

[00067] The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and diaikoxyalkyl

radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy. Terms such as "alkoxy(halo)alkyl", indicate a molecule having a terminal alkoxy that is bound to an alkyl, which is bonded to the parent molecule, while the alkyl also has a substituent halo group in a non-terminal location. In other words, both the alkoxy and the halo group are substituents of the alkyl chain.

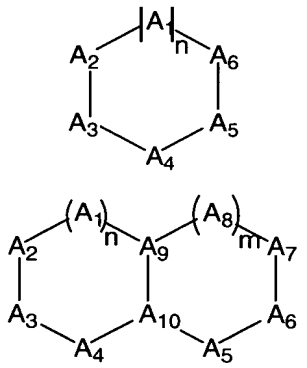
[00068] The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronapthyl, indane, and biphenyl.

[00069] The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms is replaced by N, S, P, or O. This includes, for example, structures such as:



where Z, Z^1, Z^2, or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also

termed "heteroaryl" radicals include thienyl, pyrryl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl, and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The terms aryl or heteroaryl, as appropriate, include the following structures:



where:

when n=1, m=1 and A_1-A_8 are each CR^x or N, A_9 and A_{10} are carbon;

when n=0, or 1, and m=0, or 1, one of A_2-A_4 and/or A_5-A_7 is optionally S, O, or NR^x, and other ring members are CR^x or N, with the proviso that oxygen cannot be adjacent to sulfur in a ring. A_9 and A_{10} are carbon;

when n is greater than or equal to 0, and m is greater than or equal to 0, 1 or more sets of 2 or more adjacent atoms A_1-A_{10} are sp3 O, S, NR^x, CR^xR^y, or C=(O or S), with the proviso that oxygen and sulfur cannot be adjacent. The remaining A_1-A_8 are CR^x or N, and A_9 and A_{10} are carbon;

when n is greater than or equal to 0, and m greater than or equal to 0, atoms separated by 2 atoms (*i.e.*, A_1 and A_4) are Sp3 O, S, NR^x, CR^xR^y, and remaining A_1-A_8 are independently CR^x or N, and A_9 and A_{10} are carbon.

[00070] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical,

where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2-NH_2$), which may also be termed an "aminosulfonyl". The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical.

[00071] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2-H$. The term "carboxyalkyl" embraces radicals having a carboxyradical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes – (C=O) –. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is CH_3 – (CO) –. The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(CH_3)_3$-C-O–C=O) – and – (O=)C– OCH_3. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Examples of such "alkoxycarbonylalkyl" radicals include $(CH_3)_3C$-OC(=O)-$(CH_2)_2$ – and – $(CH_2)_2$ (–O)$COCH_3$. The terms "amido", or "carbamyl", when used alone or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical. The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with

one alkylradical and with two alkyl radicals, respectively. The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkylradicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an –C(–NH)–NH_2 radical. The term "cyanoamidin" denotes an –C(–N–CN) –NH_2 radical. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl.

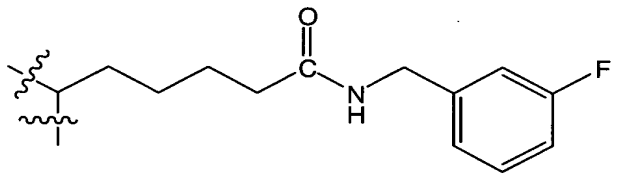
[00072] The terms "aralkyl", or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cylopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[00073] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3 –S–). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent –S(–O) – atom. The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively.

[00074] The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of

hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino (CH_3-C(=O) –NH–).

[00075] In the naming of substituent groups for general chemical structures, the naming of the chemical components of the group is typically from the terminal group-toward the parent compound unless otherwise noted, as discussed below. In other words, the outermost chemical structure is named first, followed by the next structure in line, followed by the next, etc. until the structure that is connected to the parent structure is named. For example, a substituent group having a structure such as:



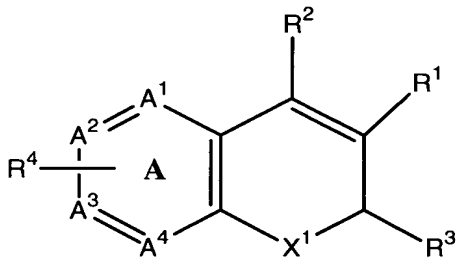
may be referred to generally as a "haloarylalkylaminocarboxylalkyl". An example of one such group would be fluorophenylmethylcarbamylpentyl. The bonds having wavy lines through them represent the parent structure to which the alkyl is attached.

[00076] Substituent groups may also be named by reference to one or more "R" groups. The structure shown above would be included in a description, such as, "-C_1-C_6-alkyl-COR^u, where R^u is defined to include -NH-C_1-C_4-alkylaryl-R^y, and where R^y is defined to include halo. In this scheme, atoms having an "R" group are shown with the "R" group being the terminal group (*i.e.*, furthest from the parent). In a term such as "$C(R^x)_2$", it should be understood that the two R^x groups can be the same, or they can be different if R^x is defined as having more than one possible identity.

[00077] In one embodiment of the present invention, the Cox-2 selective inhibitor is of the chromene/chroman structural class, which encompasses substituted benzopyrans or substituted benzopyran analogs,

as well as substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the general Formulas I, II, III, IV, V, and VI, shown below, and including, by way of non-limiting example, the structures disclosed in Table 1, and the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00078] Benzopyrans that can serve as a Cox-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent Nos. 6,271,253 and 6,492,390. One such class of compounds is defined by the general formula shown below in formula **I**:



I

wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, acyl and carboxy-C_1 –C_6 –alkyl; wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl; or wherein $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, C_1 –C_6 –alkyl and C_2 –C_6 –alkenyl;

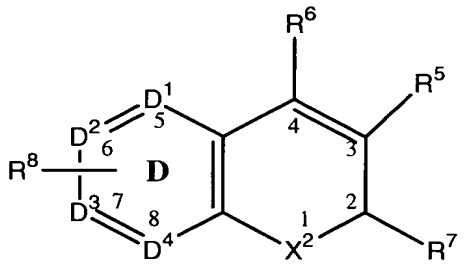
wherein R^3 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

wherein R^4 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 –alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 –C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio, C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-$_1$ –C_3 –hydroxyalkyl, C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 –C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 –C_6 –alkylaminosulfonyl, heteroaryl-C_1 –C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 –alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_1 –alkoxycarbonyl, formyl, C_1 –C_6 –haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and

wherein the A ring atoms A^1, A^2, A^3 and A^4 are independently selected from carbon and nitrogen with the proviso that at least two of A^1, A^2, A^3 and A^4 are carbon;

or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

[00079] Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes compounds having the structure of formula **II**:



II

wherein X^2 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy-C_1 –C_6 –alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

or wherein $CR^c R^b$ form a cyclopropyl ring;

wherein R^5 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^6 is selected from hydrido, phenyl, thienyl, C_2 –C_6 –alkynyl and C_2 –C_6 –alkenyl;

wherein R^7 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

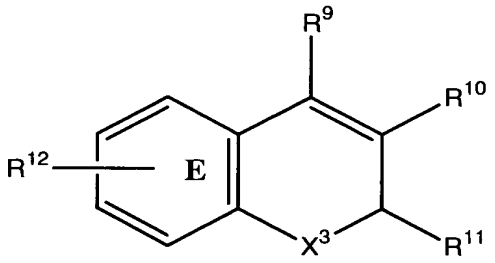
wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 –alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 –C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, —$O(CF_2)_2$ O—, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio, C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-C_1 –C_3 –hydroxyalkyl), C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 –C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl,

heteroarylaminosulfonyl, aryl-C_1 –C_6 –alkylaminosulfonyl, heteroaryl-C_1 –C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 –alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_6 –alkoxycarbonyl, formyl, C_1 –C_6 –haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and

wherein the D ring atoms D^1, D^2, D^3 and D^4 are independently selected from carbon and nitrogen with the proviso that at least two of D^1, D^2, D^3 and D^4 are carbon; or

wherein R^8 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

[00080] Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula **III**:



III

wherein X^3 is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

wherein R^9 is selected from the group consisting of H and aryl;

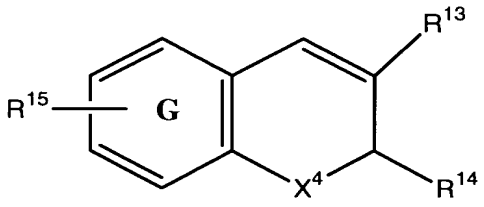
wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or

wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00081] A related class of compounds useful as Cox-2 selective inhibitors in the present invention is described by Formulas **IV** and **V** below:



IV

wherein X^4 is selected from O or S or NR^a ;

wherein R^a is alkyl;

wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

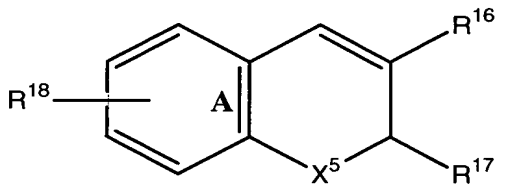
wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^{15} together with ring G forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00082] Formula **V** is:



V

wherein:

X^5 is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl,

heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00083] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00084] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

R^{17} is lower haloalkyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl,

lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00085] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R^2 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00086] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

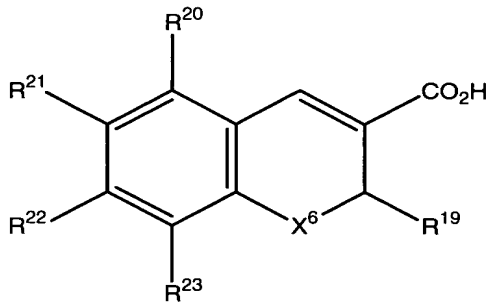
R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

[00087] The Cox-2 selective inhibitor of the present invention can also be a compound having the structure of Formula **VI**:



VI

wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is lower haloalkyl;

R^{20} is selected from the group consisting of hydrido, and halo;

R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

[00088] The Cox-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

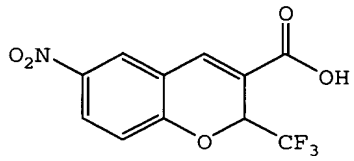
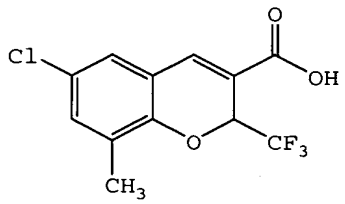
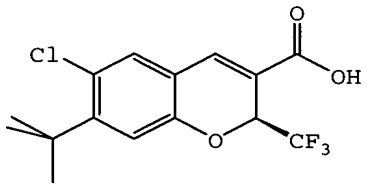
R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

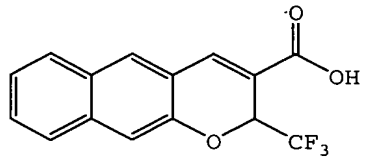
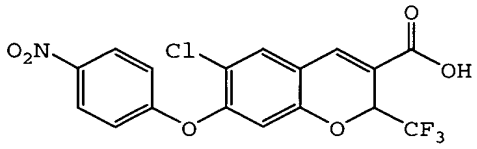
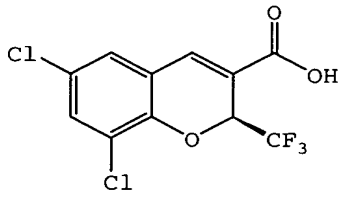
R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

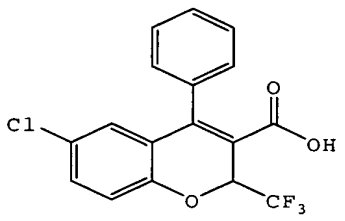
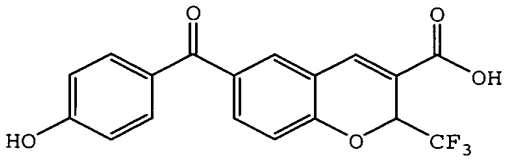
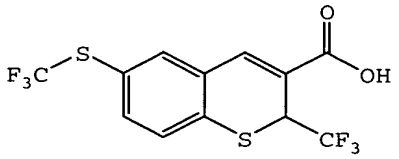
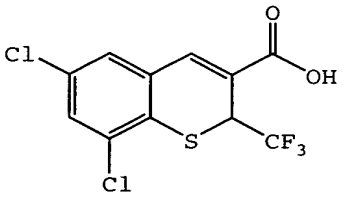
R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

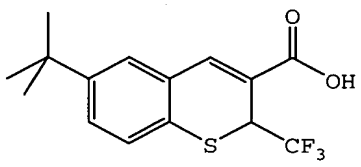
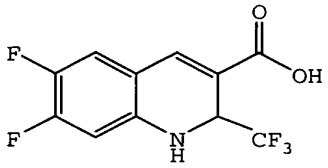
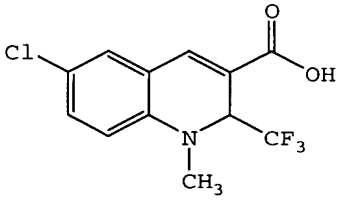
or an isomer or prodrug thereof.

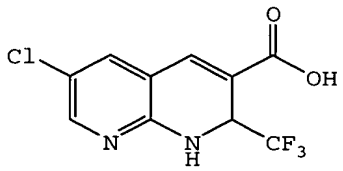
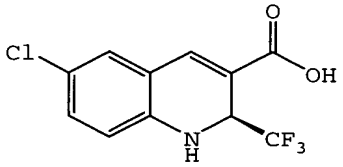
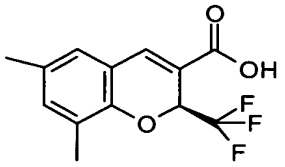
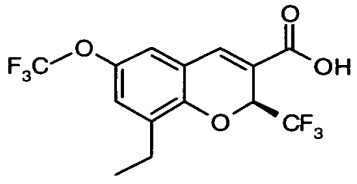
[00089] Table 1. Examples of Chromene Cox-2 Selective Inhibitors

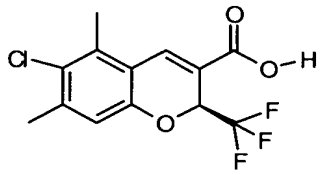
Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-18	 (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid
B-19	 (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

Compound Number	Structural Formula
B-20	 (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

[00090] In preferred embodiments, the chromene Cox-2 inhibitor is comprises at least one compound selected from the group consisting of 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid, 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

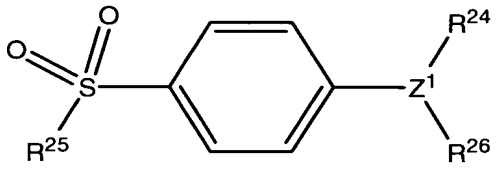
6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid,
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid,
6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-(difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
6,8-dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
5,6-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
2,6-bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

5,6,7-trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,7,8-trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
6-bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
6-chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid, and mixtures thereof.

[00091] In further preferred embodiments, the chromene Cox-2 inhibitor is selected from (S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-6-chloro-8-methyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, and mixtures thereof.

[00092] In a preferred embodiment of the invention, the Cox-2 inhibitor can be selected from the class of tricyclic Cox-2 selective inhibitors represented by the general structure of formula **VII**:



VII

wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a

substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

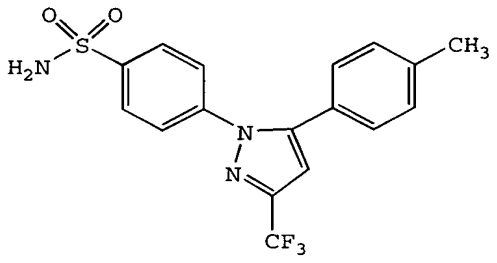
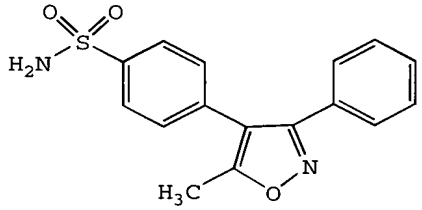
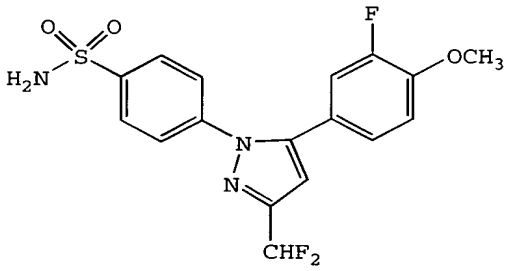
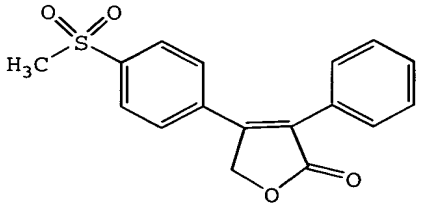
or a prodrug thereof.

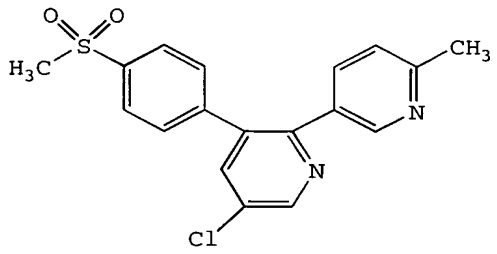
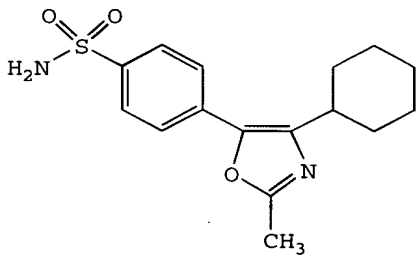
[00093] In a preferred embodiment of the invention, the tricyclic Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

[00094] In a further preferred embodiment of the invention, the Cox-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-21), valdecoxib (B-22), deracoxib (B-23), rofecoxib (B-24), etoricoxib (MK-663; B-25), JTE-522 (B-26), or prodrugs thereof.

[00095] Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

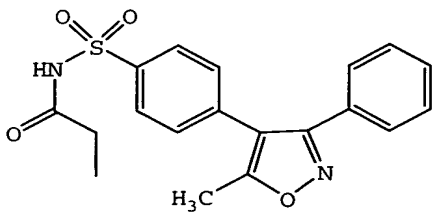
Table 2. Examples of Tricyclic Cox-2 Selective Inhibitors

Compound Number	**Structural Formula**
B-21	
B-22	
B-23	
B-24	

Compound Number	Structural Formula
B-25	
B-26	

[00096] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

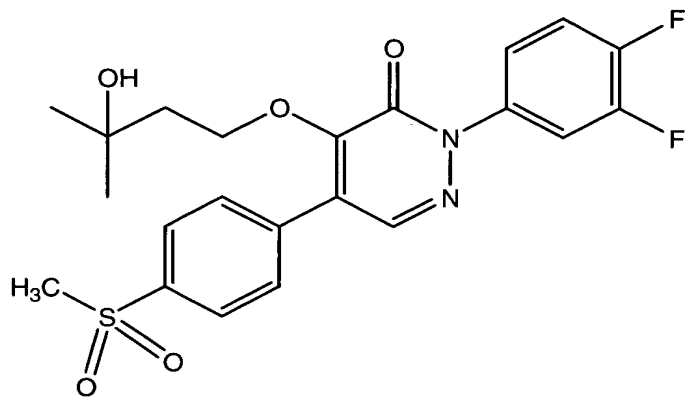
[00097] In a preferred embodiment, parecoxib (See, U.S. Patent No. 5,932,598), having the structure shown in B-27, and which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor valdecoxib, B-22, (See, U.S. Patent No. 5,633,272), may be advantageously employed as the Cox-2 inhibitor of the present invention.



B-27

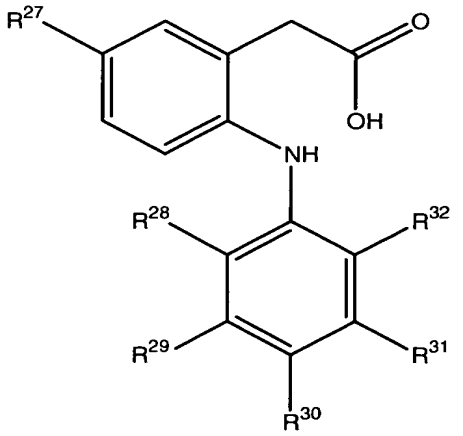
[00098] A preferred form of parecoxib is sodium parecoxib.

[00099] Another tricyclic Cox-2 selective inhibitor useful in the present invention is the compound ABT-963, having the formula B-28 shown below, that has been previously described in International Publication Number WO 00/24719.



B-28

[000100] In a further embodiment of the invention, the Cox-2 inhibitor can be selected from the class of phenylacetic acid derivative Cox-2 selective inhibitors represented by the general structure of formula **VIII**:



VIII

wherein:

R^{27} is methyl, ethyl, or propyl;

R^{28} is chloro or fluoro;

R^{29} is hydrogen, fluoro, or methyl;

R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxyl;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R^{28}, R^{29}, R^{30} and R^{31} are not all fluoro when R^{27} is ethyl and R^{30} is H.

[000101] An exemplary phenylacetic acid derivative Cox-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in formula **VIII**,

wherein:

R^{27} is ethyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

[000102] Another phenylacetic acid derivative Cox-2 selective inhibitor is a compound that has the structure shown in formula **VIII**, wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

[000103] Another phenylacetic acid derivative Cox-2 selective inhibitor that is disclosed in WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib; CAS Reg. No. 220991-20-8), having the structure shown in formula **VIII**,

wherein:

R^{27} is methyl;

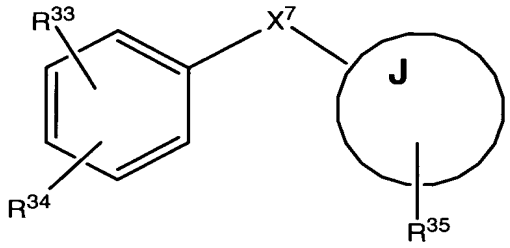
R^{28} is fluoro;

R^{32} is chloro; and

R^{29}, R^{30}, and R^{31} are hydrogen.

[000104] Compounds having a structure similar to that shown in formula **VIII**, that can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,451,858, 6,310,099, 6,291,523, and 5,958,978.

[000105] Other Cox-2 selective inhibitors that can be used in the present invention have the general structure shown in formula **IX**, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



IX

wherein:

X^7 is O; J is 1-phenyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 4-NO_2; and there is no R^{35} group, (nimesulide), or

X^7 is O; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$NHSO_2CH_3$, (flosulide); or

X^7 is O; J is cyclohexyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 5-NO_2; and there is no R^{35} group, (NS-398); or

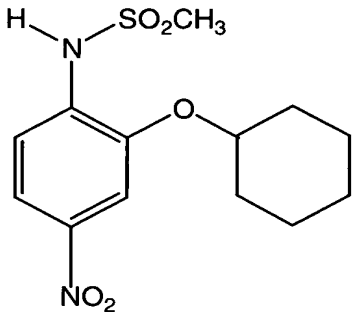
X^7 is S; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$N^-SO_2CH_3 \cdot Na^+$, (L-745337); or

X^7 is S; J is thiophen-2-yl; R^{33} is 4-F; there is no R^{34} group; and R^{35} is 5-$NHSO_2CH_3$, (RWJ-63556); or

X^7 is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R^{33} is 3-F; R^{34} is 4-F; and R^{35} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

[000106] The Cox-2 selective inhibitor NS-398, also known as N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (CAS RN 123653-11-2), having a structure as shown below in formula B-29, has been described in,

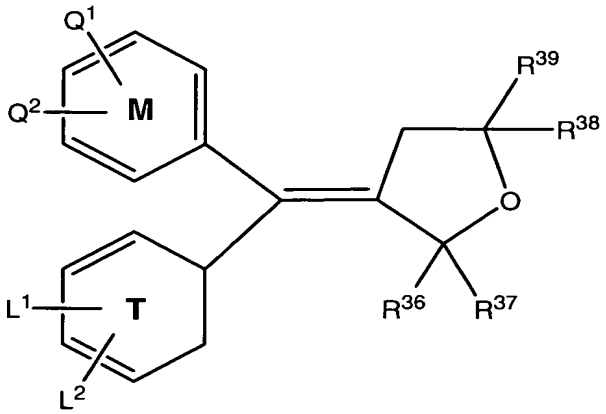
for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res., 90(4):*406 – 412 (1999).



B-29

[000107] An evaluation of the anti-inflammatory activity of the Cox-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

[000108] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **X**:



X

wherein:

the rings T and M independently are a phenyl radical, a naphthyl radical, a radical derived from a heterocycle comprising 5 to 6 members

and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q^1, Q^2, L^1 or L^2 is an —$S(O)_n$ —R group, in which n is an integer equal to 0, 1 or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an $-SO_2NH_2$ group;

and is located in the para position,

the others independently being a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a trifluoromethyl radical, or a lower O-alkyl radical having 1 to 6 carbon atoms, or Q^1 and Q^2 or L^1 and L^2 are a methylenedioxy group; and

R^{36}, R^{37}, R^{38} and R^{39} independently are a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{36}, R^{37} or R^{38}, R^{39} are an oxygen atom; or

R^{36}, R^{37} or R^{38}, R^{39}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

[000109] Particular diarylmethylidenefuran derivatives that can serve as the Cox-2 selective inhibitor of the present invention include, for example, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

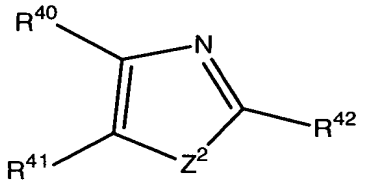
[000110] Other Cox-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367

(Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

[000111] Compounds that may act as Cox-2 selective inhibitors of the present invention include multibinding compounds containing from 2 to 10 ligands covanlently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

[000112] Conjugated linoleic, as described in U.S. Patent No. 6,077,868, is useful as a Cox-2 selective inhibitor in the present invention.

[000113] Compounds that can serve as a Cox-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such heterocyclic aromatic oxazole compounds have the formula shown below in formula **XI**:

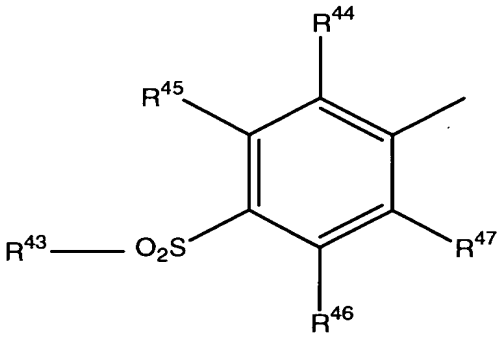


XI

wherein:

Z^2 is an oxygen atom;

one of R^{40} and R^{41} is a group of the formula



wherein:

R^{43} is lower alkyl, amino or lower alkylamino; and

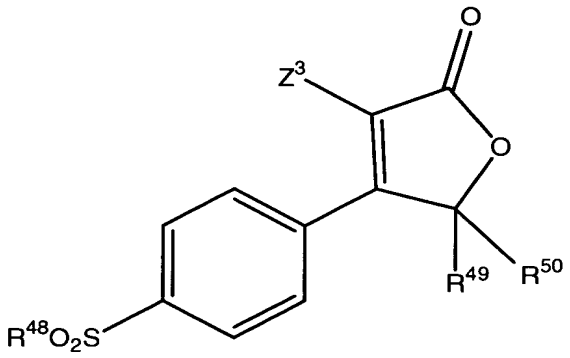
R^{44}, R^{45}, R^{46} and R^{47} are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxyl or amino,

provided that at least one of R^{44}, R^{45}, R^{46} and R^{47} is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

R^{30} is a lower alkyl or a halogenated lower alkyl,

and a pharmaceutically acceptable salt thereof.

[000114] Cox-2 selective inhibitors that are useful in the method and compositions of the present invention include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by formula **XII**:



XII

wherein:

Z^3 is selected from the group consisting of linear or branched C_1 – C_6 alkyl, linear or branched C_1 –C_6 alkoxy, unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from

the group consisting of hydrogen, halo, C_1 –C_3 alkoxy, CN, C_1 –C_3 fluoroalkyl C_1 –C_3 alkyl, and –CO_2 H;

R^{48} is selected from the group consisting of NH_2 and CH_3,

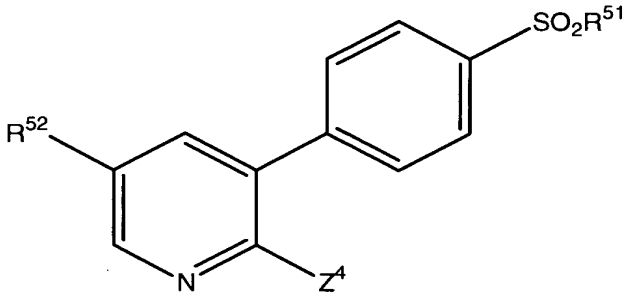
R^{49} is selected from the group consisting of C_1 –C_6 alkyl unsubstituted or substituted with C_3 –C_6 cycloalkyl, and C_3 –C_6 cycloalkyl;

R^{50} is selected from the group consisting of:

C_1 –C_6 alkyl unsubstituted or substituted with one, two or three fluoro atoms, and C_3 –C_6 cycloalkyl;

with the proviso that R^{49} and R^{50} are not the same.

[000115] Pyridines that are described in U.S. Patent Nos. 6,596,736, 6,369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and can serve as Cox-2 selective inhibitors of the present invention, have the general formula described by formula **XIII**:



XIII

wherein:

R^{51} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

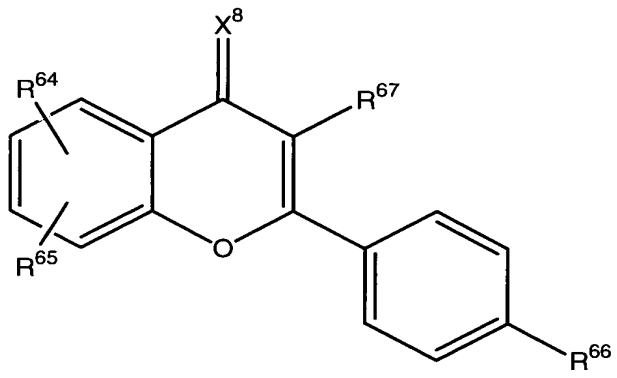
Z^4 is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof), wherein the substituents are chosen from the group consisting of hydrogen, halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, –CO_2R^{53}, hydroxyl, –$C(R^{54})(R^{55})$—OH, – C_1 – C_6 alkyl-CO_2—R^{56}, C_1 –C_6 fluoroalkoxy;

R^{52} is chosen from the group consisting of: halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, —CO_2R^{57}, hydroxyl, —$C(R^{58})(R^{59})$—OH, — C_1 –C_6 alkyl-CO_2—R^{60}, C_1 –C_6 fluoroalkoxy, NO_2, $NR^{61}R^{62}$, and $NHCOR^{63}$;

R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, and R^{63}, are each independently chosen from the group consisting of hydrogen andC_1 –C_6 alkyl;

or R^{54} and R^{55}, R^{58} and R^{59}, or R^{61} and R^{62} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

[000116] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula **XIV**:



XIV

wherein:

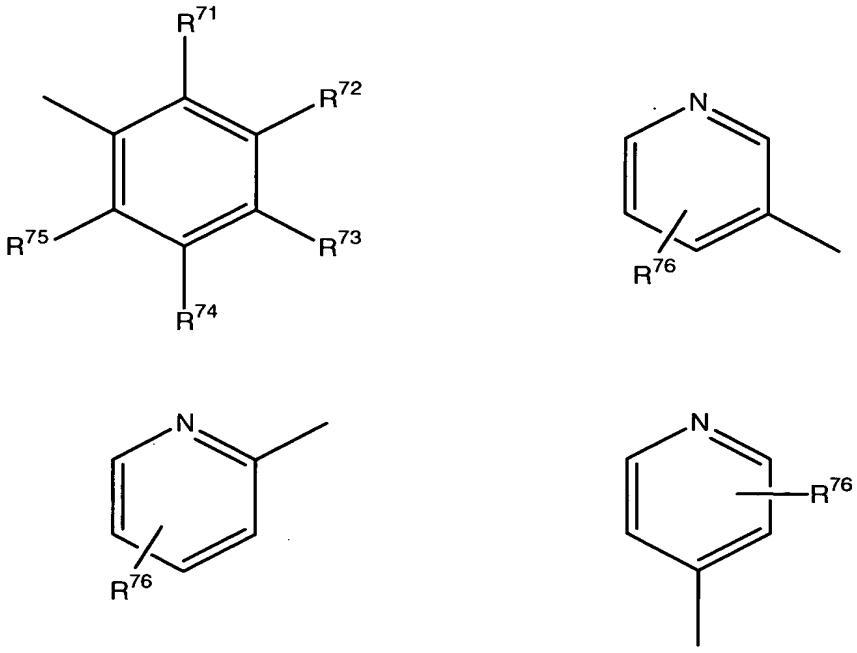
X^8 is an oxygen atom or a sulfur atom;

R^{64} and R^{65}, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a nitro group, a nitrile group, or a carboxyl group;

R^{66} is a group of a formula: $S(O)_nR^{68}$ wherein n is an integer of 0~2,

R^{68} is a hydrogen atom, a C_1 –C_6 lower alkyl group, or a group of a formula: NR^{69} R^{70} wherein R^{69} and R^{70}, identical to or different from each other, are independently a hydrogen atom, or a C_1 –C_6 lower alkyl group; and

R^{67} is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C_1 –C_6 lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:

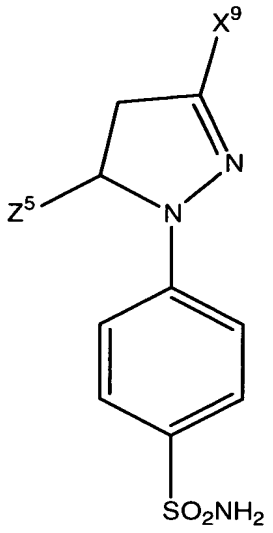


wherein:

R^{71} through R^{75}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: NR^{69} R^{70}, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,
wherein n, R^{68}, R^{69} and R^{70} have the same meaning as defined by R^{66} above; and

R^{76} is a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.

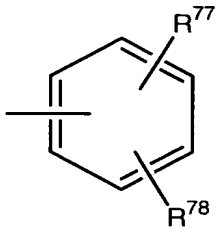
[000117] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula **XV**:



XV

wherein:

X^9 is selected from the group consisting of C_1 –C_6 trihalomethyl, preferably trifluoromethyl; C_1 –C_6 alkyl; and an optionally substituted or di-substituted phenyl group of formula **XVI**:



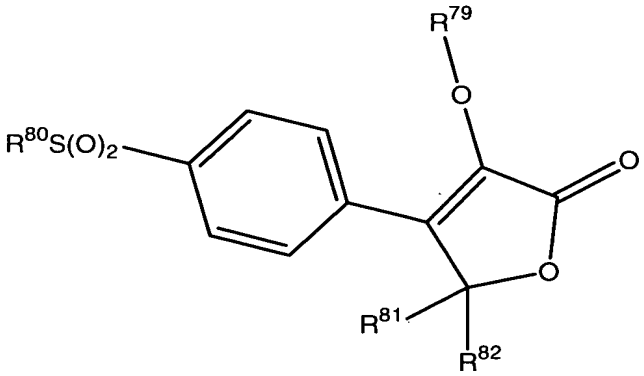
XVI

wherein:

R^{77} and R^{78} are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C_1 –C_6 alkyl, preferably C_1 –C_3 alkyl; C_1 –C_6 alkoxy, preferably C_1 – C_3 alkoxy; carboxy; C_1 –C_6 trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

[000118] Compounds useful as Cox-2 selective inhibitors of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



XVII

wherein:

R^{79} is a mono-, di-, or tri-substituted C_1 –C_{12} alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10}

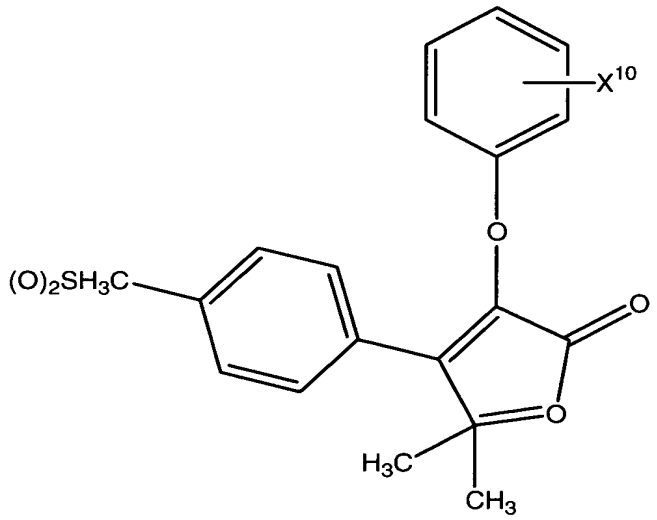
alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10} alkynyl, or an unsubstituted or mono-, di- or tri-substituted C_3 –C_{12} cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted C_5 –C_{12} cycloalkynyl, wherein the substituents are chosen from the group consisting of halo selected from F, Cl, Br, and I, OH, CF_3, C_3 – C_6 cycloalkyl, =O,dioxolane, CN;

R^{80} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

R^{81} and R^{82} are independently chosen from the group consisting of hydrogen and C_1 –C_{10} alkyl;

or R^{81} and R^{82} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

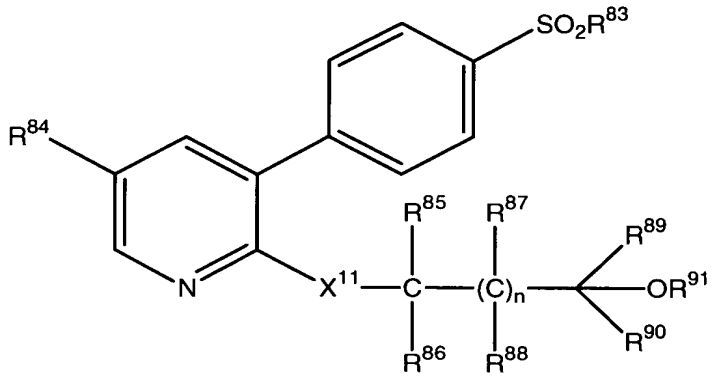
[000119] Formula **XVIII** is:



XVIII

wherein X^{10} is fluoro or chloro.

[000120] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



XIX

or a pharmaceutically acceptable salt thereof,

wherein:

X^{11} is selected from the group consisting of O, S, and a bond;

n is 0 or 1;

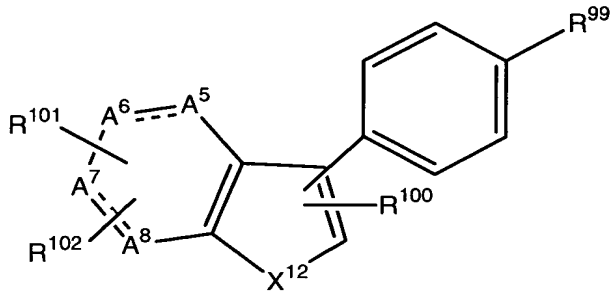
R^{83} is selected from the group consisting of CH_3, NH_2, and $NHC(O)CF_3$;

R^{84} is chosen from the group consisting of halo, C_1 –C_6 alkoxy, C_1 – C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, —CO_2 R^{92}, hydroxyl, —$C(R^{93})(R^{94})$—OH, —C_1 –C_6 alkyl-CO_2 —R^{95}, C_1 –C_6 fluoroalkoxy, NO_2, NR^{96} R^{97}, and $NHCOR^{98}$;

R^{85} to R^{89} are independently chosen from the group consisting of hydrogen and C_1 –C_6 alkyl;

or R^{85} and R^{89}, or R^{89} and R^{90} together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R^{85} and R^{87} are joined to form a bond.

[000121] Compounds that are useful as the Cox-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula **XX**:



XX

and pharmaceutically acceptable salts thereof wherein:

$—A^5=A^6—A^7=A^8—$ is selected from the group consisting of:

(a) —CH=CH—CH=CH—,

(b) $—CH_2—CH_2—CH_2—C(O)—$, $—CH_2—CH_2—C(O)—CH_2—$, $—CH_2—C(O)—CH_2—CH_2$, $—C(O)—CH_2—CH_2—CH_2$,

(c) $—CH_2—CH_2—C(O)—$, $—CH_2—C(O)—CH_2—$, $—C(O)—CH_2—CH_2—$

(d) $—CH_2—CH_2—O—C(O)—$, $CH_2—O—C(O)—CH_2—$, $—O—C(O)—CH_2—CH_2—$,

(e) $—CH_2—CH_2—C(O)—O—$, $—CH_2—C(O)—OCH_2—$, $—C(O)—O—CH_2—CH_2—$,

(f) $—C(R^{105})_2—O—C(O)—$, $—C(O)—O—C(R^{105})_2—$, $—O—C(O)—C(R^{105})_2—$, $—C(R^{105})_2—C(O)—O—$,

(g) —N=CH—CH=CH—,

(h) —CH=N—CH=CH—,

(i) —CH=CH—N=CH—,

(j) —CH=CH—CH=N—,

(k) —N=CH—CH=N—,

(l) —N=CH—N=CH—,

(m) —CH=N—CH=N—,

(n) —S—CH=N—,

(o) —S—N=CH—,

(p) —N=N—NH—,

(q) —CH=N—S—, and

(r) —N=CH—S—;

R^{99} is selected from the group consisting of $S(O)_2CH_3$, $S(O)_2NH_2$, $S(O)_2NHCOCF_3$, $S(O)(NH)CH_3$, $S(O)(NH)NH_2$, $S(O)(NH)NHCOCF_3$, $P(O)(CH_3)OH$, and $P(O)(CH_3)NH_2$;

R^{100} is selected from the group consisting of:

(a) C_1 –C_6 alkyl,

(b) C_3 –C_7 cycloalkyl,

(c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo, including F, Cl, Br, I,

(3) C_1 –C_6 alkoxy,

(4) C_1 –C_6 alkylthio,

(5) CN,

(6) CF_3,

(7) C_1 –C_6 alkyl,

(8) N_3,

(9) —CO_2 H,

(10) —CO_2 —C_1 –C_4 alkyl,

(11) —$C(R^{103})(R^{104})$—OH,

(12) —$C(R^{103})(R^{104})$—O—C_1 –C_4 alkyl, and

(13) —C_1 –C_6 alkyl-CO_2 —R^{106};

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{103})(R^{104})$—OH, and

(10) —$C(R^{103})(R^{104})$—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{101} and R^{102} are the substituents residing on any position of –A^5=A^6—A^7=A^8— and are selected independently from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) —Q^3 wherein Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})$OH,

(f) —O—Q^4,

(g) —S—Q^4, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^3,

(2) —O—C_1 –C_5 alkyl-Q^3,

(3) —S—C_1 –C_5 alkyl-Q^3,

(4) —C_1 –C_3 alkyl-O—C_{1-3} alkyl-Q^3,

(5) —C_1 –C_3 alkyl-S—C_{1-3} alkyl-Q^3,

(6) —C_1 –C_5 alkyl-O—Q^4,

(7) —C_1 –C_5 alkyl-S—Q^4,

wherein the substituent resides on the alkyl chain and the substituent is C_1 –C_3 alkyl, and Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})$OH Q^4 is CO_2 —C_1 –C_4 alkyl, tetrazolyl-5-yl, or $C(R^{103})(R^{104})$O—C_1 –C_4 alkyl;

R^{103}, R^{104} and R^{105} are each independently selected from the group consisting of hydrogen and C_1 –C_6 alkyl; or

R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two

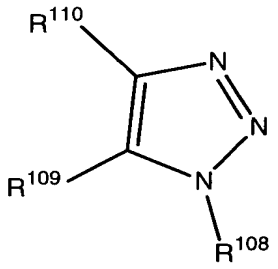
R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_1 –C_6 alkyl;

R^{107} is hydrogen, C_1 –C_6 alkyl or aryl;

X^7 is O, S, NR^{107}, CO, $C(R^{107})_2$, $C(R^{107})(OH)$, —$C(R^{107})$=$C(R^{107})$—; —$C(R^{107})$=N—; or —N=$C(R^{107})$—.

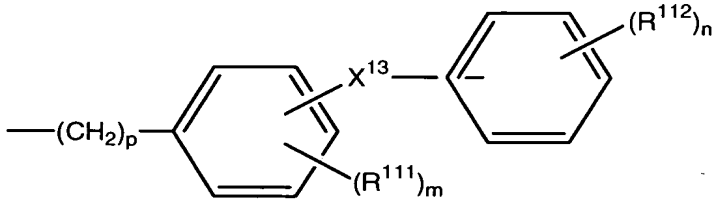
[000122] Compounds that may act as Cox-2 selective inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula **XXI**:



XXI

wherein:

R^{108} is:



wherein:

p is 0 to 2; m is 0 to 4; and n is 0 to 5;

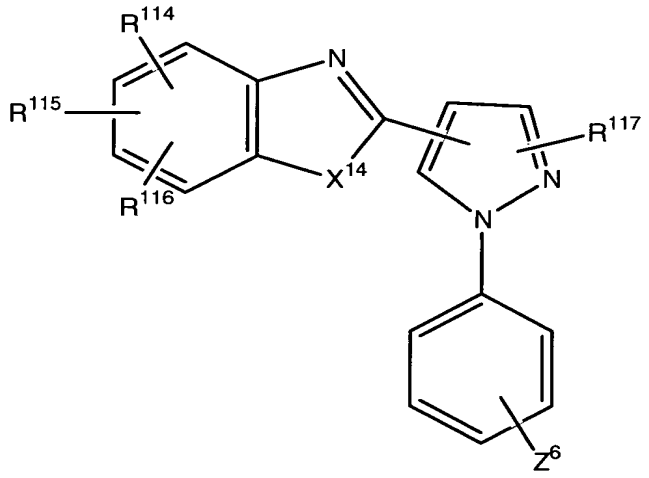
X^{13} is O, S, SO, SO_2, CO, CHCN, CH_2 or C=NR^{113} where R^{113} is hydrogen, loweralkyl, hydroxyl, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano;

R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl, loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifuloromethoxy, acetamido, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl;

R^{109} is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, or guanidino; and

R^{110} is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; wherein the loweralkyl, loweralkyl containing, loweralkoxy and loweralkanoyl groups contain from 1 to 3 carbon atoms.

[000123] Pyrazole derivatives such as those described in U.S. Patent 6,136,831 can serve as a Cox-2 selective inhibitor of the present invention. Such pyrazole derivatives have the formula shown below in formula **XXII**:



XXII

wherein:

R^{114} is hydrogen or halogen;

R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxyl or lower alkanoyloxy;

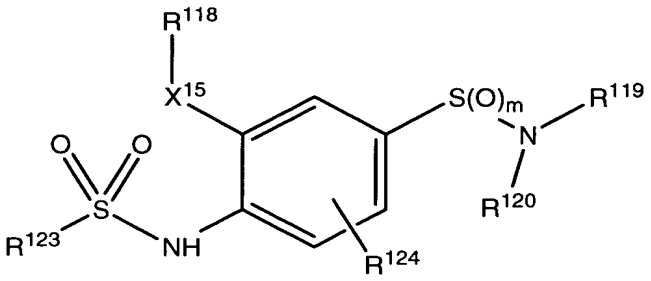
R^{117} is lower haloalkyl or lower alkyl;

X^{14} is sulfur, oxygen or NH; and

Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable salt thereof.

[000124] Materials that can serve as a Cox-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



XXIII

wherein:

X^{15} denotes oxygen, sulphur or NH;

R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy;

R^{119} and R^{120}, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$ $-X^{16}$; or

R^{119} and R^{120}, together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$—X^{16};

X^{16} denotes halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2 R^{121}, —OCO_2 R^{121}, —CN, —$CONR^{121}$ OR^{122}, —$CONR^{121}$ R^{122}, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2$ R^{121}, —NR^{121} R^{122}, —$NHC(O)R^{121}$, —$NHS(O)_2$ R^{121};

n denotes a whole number from 0 to 6;

R^{123} denotes a straight-chained or branched alkyl group with 1-10 C- atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl

group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;

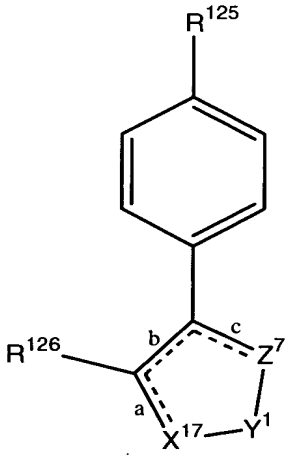
R^{124} denotes halogen, hydroxyl, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen, NO_2, —OR^{121}, —COR^{121}, —$CO_2 R^{121}$, —$OCO_2 R^{121}$, —CN, —$CONR^{121} OR^{122}$, —$CONR^{121} R^{122}$, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2 R^{121}$, —$NR^{121} R^{122}$, —$NHC(O)R^{121}$, —$NHS(O)_2 R^{121}$, or a polyfluoroalkyl group;

R^{121} and R^{122}, independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

m denotes a whole number from 0 to 2;

and the pharmaceutically-acceptable salts thereof.

[000125] Compounds that are useful as Cox-2 selective inhibitors of the present invention include phenyl heterocycles that are described in U.S. Patent Nos. 5,474,995 and 6,239,173. Such phenyl heterocyclic compounds have the formula shown below in formula **XXIV**:



XXIV

or pharmaceutically acceptable salts thereof wherein:

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) —$CH_2 CH_2 CH_2$ —,

(b) —$C(O)CH_2 CH_2$ —,

(c) —$CH_2 CH_2 C(O)$—,

(d) —CR^{129} ($R^{129'}$)—O—C(O)—,

(e) —C(O)—O—CR^{129} ($R^{129'}$)—,

(f) —CH_2 —NR^{127} —CH_2 —,

(g) —CR^{129} ($R^{129'}$)—NR^{127} —C(O)—,

(h) —CR^{128}=$CR^{128'}$ —S—,

(i) —S—CR^{128}=$CR^{128'}$ —,

(j) —S—N=CH—,

(k) —CH=N—S—,

(l) —N=CR^{128} —O—,

(m) —O—CR^{128} =N— ,

(n) —N=CR^{128} —NH—,

(o) —N=CR^{128} —S—, and

(p) —S—CR^{128}=N—,

(q) —C(O)—NR^{127} —CR^{129} ($R^{129'}$)—,

(r) —R^{127} N—CH=CH— provided R^{122} is not —$S(O)_2CH_3$,

(s) —CH=CH—NR^{127} — provided R^{125} is not —$S(O)_2CH_3$;

when side b is a double bond, and sides a and c are single bonds; and

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) =CH—O—CH=, and

(b) =CH—NR^{127} —CH=,

(c) =N—S—CH=,

(d) =CH—S—N=,

(e) =N—O—CH=,

(f) =CH—O—N=,

(g) =N—S—N=,

(h) =N—O—N=,

when sides a and c are double bonds and side b is a single bond;

R^{125} is selected from the group consisting of:

(a) $S(O)_2$ CH_3,

(b) $S(O)_2$ NH_2,

(c) $S(O)_2$ $NHC(O)CF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHC(O)CF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{126} is selected from the group consisting of

(a) C_1 –C_6 alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_1 –C_6 alkoxy,

(4) C_1 –C_6 alkylthio,

(5) CN,

(6) CF_3,

(7) C_1 –C_6 alkyl,

(8) N_3,

(9) —CO_2 H,

(10) —CO_2 —C_1 –C_4 alkyl,

(11) —$C(R^{129})(R^{130})$—OH,

(12) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl, and

(13) —C_1 –C_6 alkyl-CO_2 —R^{129} ;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{129})(R^{130})$—OH, and

(10) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{127} is selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) hydroxyl C_1 –C_6 alkyl,

(f) —C(O)— C_1 –C_6 alkyl,

(g) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —C_1 –C_5 alkyl-O—C_1 –C_3 alkyl-Q^5,

(3) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(4) —C_1 –C_5 alkyl-O—Q^5, or

(5) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl;

(h) –Q^5;

R^{128} and $R^{128'}$ are each independently selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) –Q^5,

(f) —O—Q^5;

(g) —S—Q^5, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —O—C_1 –C_5 alkyl-Q^5,

(3) —S—C_1 –C_5 alkyl-Q^5,

(4) —C_1 –C_3 alkyl-O—C_1 –C_3 alkyl-Q^5,

(5) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(6) —C_1 –C_5 alkyl-O—Q^5,

(7) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl, and

R^{129}, $R^{129'}$, R^{130}, R^{131} and R^{132} are each independently selected from the group consisting of:

(a) hydrogen,

(b) C_1 –C_6 alkyl;

or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

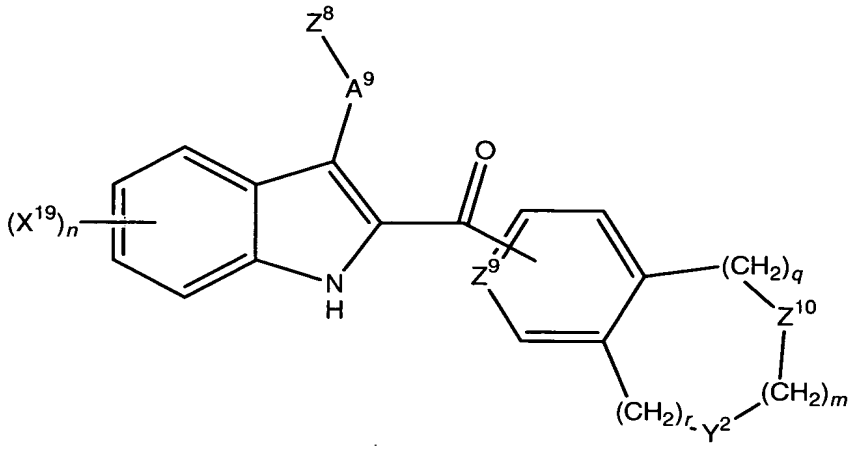
Q^5 is CO_2 H, CO_2 —C_1 –C_4 alkyl, tetrazolyl-5-yl, $C(R^{131})(R^{132})(OH)$, or

$C(R^{131})(R^{132})(O—C_1 –C_4$ alkyl);

provided that when X—Y—Z is —S—CR^{128}=$CR^{128'}$, then R^{128} and $R^{128'}$ are other than CF_3.

[000126] An exemplary phenyl heterocycle that is disclosed in U.S. Patent No. 6,239,173 is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(2H)-furanone.

[000127] Bicycliccarbonyl indole compounds such as those described in U.S. Patent No. 6,303,628 are useful as Cox-2 selective inhibitors of the present invention. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



XXV

or the pharmaceutically acceptable salts thereof wherein:

A^9 is C_1 –C_6 alkylene or —NR^{133} —;

Z^8 is $C(=L^3)R^{134}$, or SO_2 R^{135} ;

Z^9 is CH or N;

Z^{10} and Y^2 are independently selected from —CH_2 —, O, S and —N—R^{133};

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

X^{18} is independently selected from halogen, C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkoxy, C_1 –C_4 alkylthio, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino and cyano;

n is 0, 1, 2, 3 or 4;

L^3 is oxygen or sulfur;

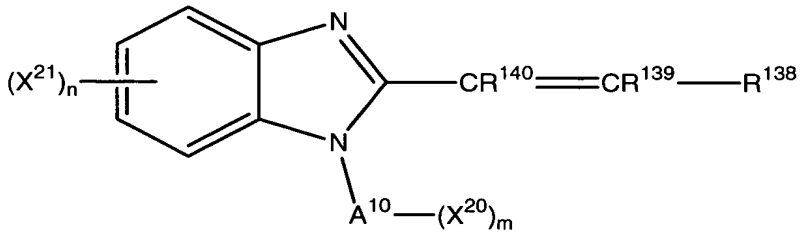
R^{133} is hydrogen or C_1 –C_4 alkyl;

R^{134} is hydroxyl, C_1 –C_6 alkyl, halo-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, halo-substituted C_1 –C_6 alkoxy, C_3 –C_7 cycloalkoxy, C_1 –C_4 alkyl(C_3 –C_7 cycloalkoxy), —NR^{136} R^{137}, C_1 –C_4 alkylphenyl-O— or phenyl-O—, said phenyl being optionally substituted with one to five substituents independently selected from halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy and nitro;

R^{135} is C_1 –C_6 alkyl or halo-substituted C_1 –C_6 alkyl; and

R^{136} and R^{137} are independently selected from hydrogen, C_{1-6} alkyl and halo-substituted C_1 –C_6 alkyl.

[000128] Materials that can serve as a Cox-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula **XXVI**:



XXVI

or a pharmaceutically acceptable salt thereof, wherein:

A^{10} is heteroaryl selected from

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or

a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

X^{20} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amonio, N-(C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)amino, N-[(C_1 –C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbamoyl, [N-(C_1 –C_4 alkyl)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro,

mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

X^{21} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-(C_1 –C_4 alkyl)-N-(C_1 –C_4 alkanoyl) amino, N-[(C_1 –C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)hydroxyl, cabamoyl, [N-(C_1 –C_4 alkyl) amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

R^{138} is selected from:

hydrogen;

straight or branched C_1 –C_4 alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

C_3 –C_8 cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are indepently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

C_4 –C_8 cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, □ydroxyl-

substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-[C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)]amino, N-[(C_1 –C_4 alkyl)sulfony]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbomoyl, [N-(C_1 –C_4 alky)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl; and

heteroaryl selected from:

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and

said heteroaryl being optionally substituted with one to three substituent(s) selected from X^{20} ;

R^{139} and R^{140} are independently selected from:

hydrogen;

halo;

C_1 –C_4 alkyl;

phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

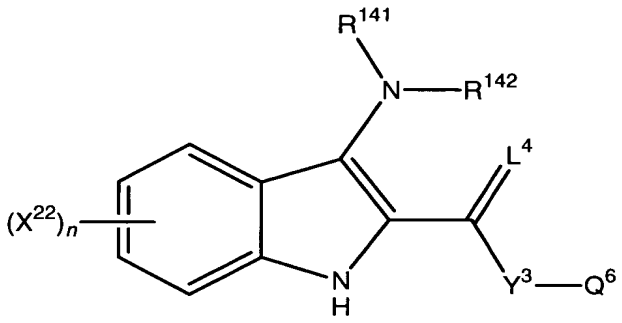
or R^{138} and R^{139} can form, together with the carbon atom to which they are attached, a C_3 –C_7 cycloalkyl ring;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4.

[000129] Compounds that may be employed as a Cox-2 selective inhibitor of the present invention include indole compounds that are

described in U.S. Patent No. 6,300,363. Such indole compounds have the formula shown below in formula **XXVII**:



XXVII

and the pharmaceutically acceptable salts thereof, wherein:

L^4 is oxygen or sulfur;

Y^3 is a direct bond or C_1 –C_4 alkylidene;

Q^6 is:

(a) C_1 –C_6 alkyl or halosubstituted C_1 –C_6 alkyl, said alkyl being optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkoxy, amino and mono- or di-(C_1 –C_4 alkyl)amino,

(b) C_3 –C_7 cycloalkyl optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkyl and C_1 –C_4 alkoxy,

(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:

(c-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_1$ –C_4 alkyl)$_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$ and —O—Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C_1 –C_4 alkyl, CF_3, hydroxyl, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino and CN;

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to

three N atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substitutents independently selected from:

(d-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, C_1 –C_4 alkyl-OH, $S(O)_m$ R^{143}, SO_2 NH_2, SO_2 $N(C_1$ –C_4 alkyl$)_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2$ R^{143}, $NHC(O)R^{143}$, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl$)_2$, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF_3, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, OCF_3, SR^{143}, SO_2 CH_3, SO_2 NH_2, amino, C_{1-4} alkylamino and $NHSO_2$ R^{143};

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

R^{141} is hydrogen or C_1 –C_6 alkyl optionally substituted with a substituent selected independently from hydroxyl, OR^{143}, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl$)_2$;

R^{142} is:

(a) hydrogen,

(b) C_1 –C_4 alkyl,

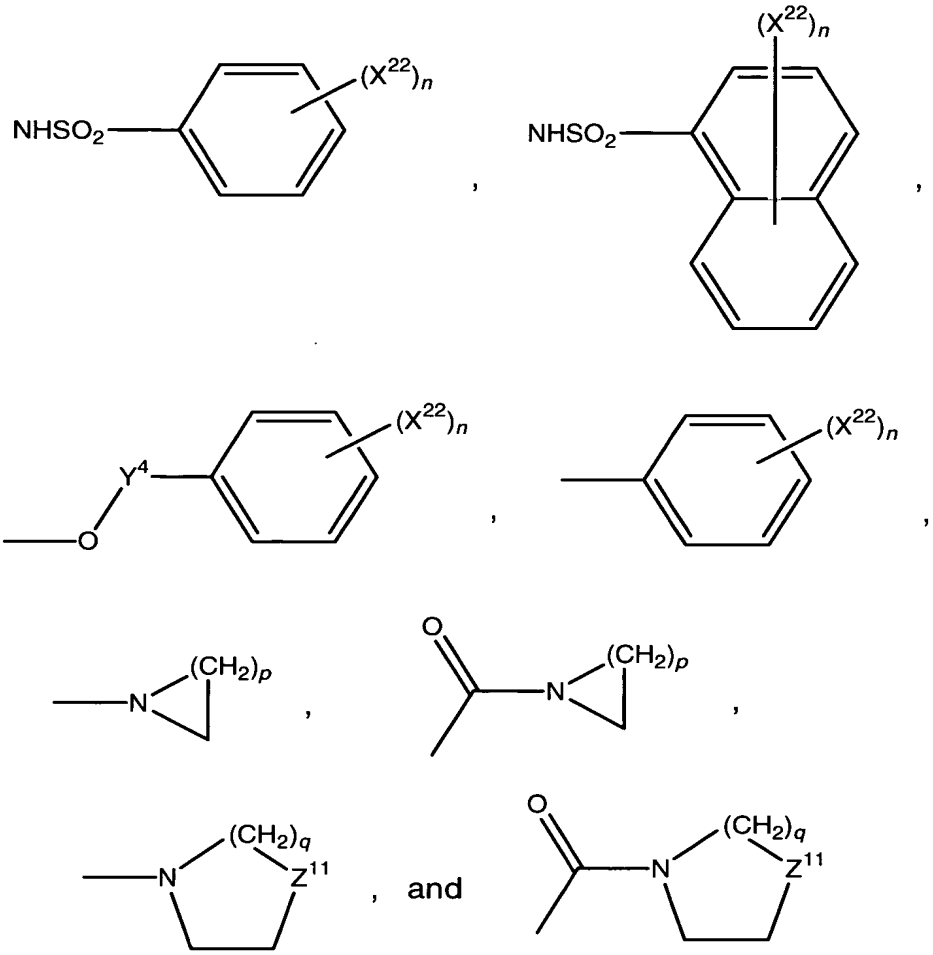
(c) $C(O)R^{145}$,

wherein R^{145} is selected from:

(c-1) C_1 –C_{22} alkyl or C_2 –C_{22} alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently selected from:

(c-1-1) halo, hydroxyl, OR^{143}, $S(O)_m$ R^{143}, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2$ R^{143}, CO_2 H, CO_2 (C_1 –C_4 alkyl), $CONH_2$,

$CONH(C_1-C_4\ alkyl)$, $CON(C_1-C_4\ alkyl)_2$, $OC(O)R^{143}$, thienyl, naphthyl and groups of the following formulas:



(c-2) C_1-C_{22} alkyl or C_2-C_{22} alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

(c-3) $-Y^5-C_3-C_7$ cycloalkyl or $-Y^5-C_3-C_7$ cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1) C_1-C_4 alkyl, hydroxyl, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_1-C_4 alkyl)amino, $CONH_2$, $CONH(C_1-C_4\ alkyl)$ and $CON(C_1-C_4\ alkyl)_2$,

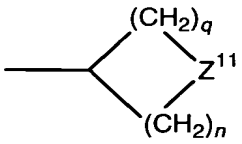
(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

(c-4-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, halosubstituted C_1 –C_8 alkyl, halosubstituted C_1 –C_8 alkoxy, CN, nitro, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 NH(C_1$ –C_4 alkyl), $SO_2 N(C_1$ –C_4 alkyl)$_2$, amino, C_1 –C_4 alkylamino, di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, $OC(O)R^{143}$, and phenyl optionally substituted with up to three substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, OCH_3, CF_3, OCF_3, CN, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl) and $CONH_2$,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, CO_2 H and CO_2 (C_1 –C_4 alkyl), and —Y-phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$,

(c-6) a group of the following formula:



X^{22} is halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstitutued C_1 –C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2$

R^{143}, nitro, halosubstitutued C_1 –C_4 alkyl, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkylOR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl) or $CON(C_1$ –C_4 alkyl)$_2$;

R^{143} is C_1 –C_4 alkyl or halosubstituted C_1 –C_4 alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;

Z^{11} is oxygen, sulfur or NR^{144} ; and

R^{144} is hydrogen, C_1 –C_6 alkyl, halosubstitutued C_1 –C_4 alkyl or –Y^5-phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, $S(O)_m$ R^{143}, amino, mono- or di-(C_1 –C_4 alkyl)amino, CF_3, OCF_3, CN and nitro;

with the proviso that a group of formula –Y^5—Q is not methyl or ethyl when

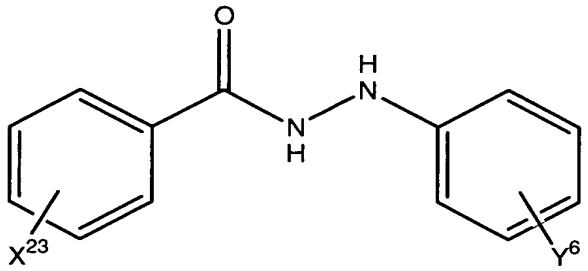
X^{22} is hydrogen;

L^4 is oxygen;

R^{141} is hydrogen; and

R^{142} is acetyl.

[000130] Aryl phenylhydrazides that are described in U.S. Patent No. 6,077,869 can serve as Cox-2 selective inhibitors of the present invention. Such aryl phenylhydrazides have the formula shown below in formula **XXVIII**:



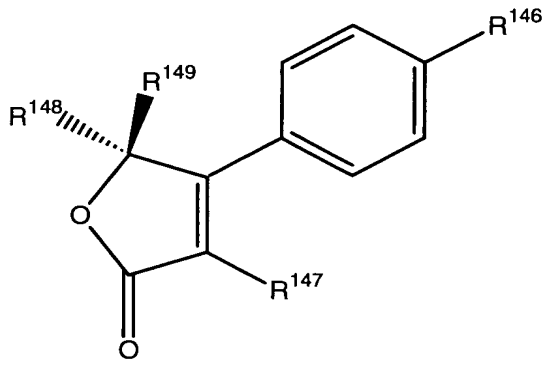
XXVIII

wherein:

X^{23} and Y^6 are selected from hydrogen, halogen, alkyl, nitro, amino, hydroxy, methoxy and methylsulfonyl;

or a pharmaceutically acceptable salt thereof,.

[000131] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula **XXIX**:



XXIX

or a pharmaceutical salt thereof, wherein:

R^{146} is selected from the group consisting of SCH_3, $—S(O)_2 CH_3$ and $—S(O)_2 NH_2$;

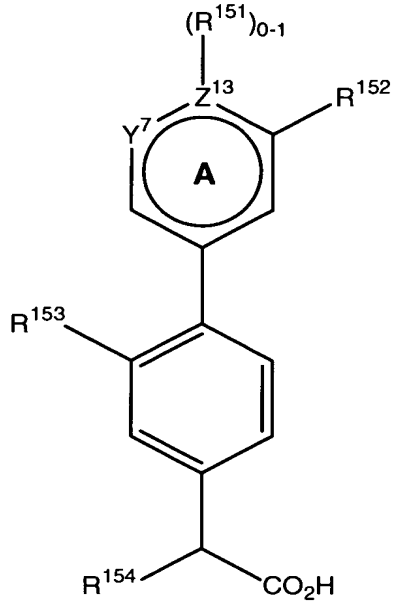
R^{147} is selected from the group consisting of OR^{150}, mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{148} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

R^{149} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

[000132] Materials that can serve as a Cox-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula **XXX**:



XXX

or a pharmaceutically acceptable salt, ester or tautomer thereof, wherein:

Z^{13} is C or N;

when Z^{13} is N, R^{151} represents H or is absent, or is taken in conjunction with R^{152} as described below:

when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristics:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can adopt an energetically stable transoid configuration and if a double bond is present, the bond is in the trans configuration,

(b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

or R^{151} and R^{152} are taken in combination and represent a 5- or 6-membered aromatic or non-aromatic ring D fused to ring A, said ring D containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an

energetically stable configuration planar with ring A to within about 15 degrees;

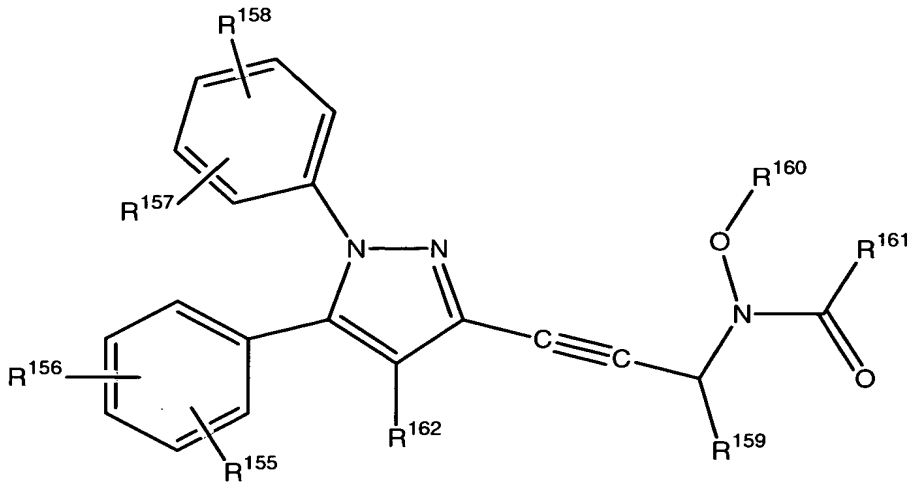
said ring D further being substituted with 1 R^a group selected from the group consisting of: C_1 –C_2 alkyl, —OC_1 –C_2 alkyl, —NHC_1 –C_2 alkyl, —$N(C_1$ –C_2 alkyl$)_2$, —C(O) C_1 –C_2 alkyl, —S—C_1 –C_2 alkyl and —C(S) C_1 –C_2 alkyl;

Y^7 represents N, CH or C—OC_1 –C_3 alkyl, and when Z^{13} is N, Y^7 can also represent a carbonyl group;

R^{153} represents H, Br, Cl or F; and

R^{154} represents H or CH_3.

[000133] Compounds useful as Cox-2 selective inhibitors of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula shown below in formula **XXXI**:



XXXI

wherein:

R^{155}, R^{156}, R^{157}, and R^{158} are independently selected from the groups consisting of hydrogen, C_1 –C_5 alkyl, C_1 –C_5 alkoxy, phenyl, halo, hydroxyl, C_1 –C_5 alkylsulfonyl, C_1 –C_5 alkylthio, trihaloC_1 –C_5 alkyl, amino, nitro and 2-quinolinylmethoxy;

R^{159} is hydrogen, C_1 –C_5 alkyl, trihaloC_1 –C_5 alkyl, phenyl, substituted phenyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro or R^{159} is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;

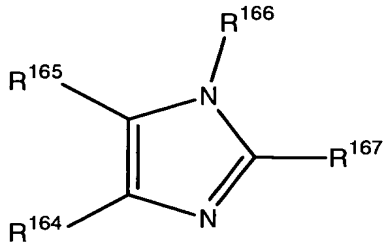
R^{160} is hydrogen, C_1 –C_5 alkyl, phenyl C_1 –C_5 alkyl, substituted phenyl C_1 –C_5 alkyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro, or R^{160} is C_1 –C_5 alkoxycarbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro;

R^{161} is C_1 –C_{10} alkyl, substituted C_1 –C_{10} alkyl where the substituents are halogen, trihaloC_1 –C_5 alkyl, C_1 –C_5 alkoxy, carboxy, C_1 –C_5 alkoxycarbonyl, amino, C_1 –C_5 alkylamino, diC_1 –C_5 alkylamino, diC_1 –C_5 alkylaminoC_1 –C_5 alkylamino, C_1 –C_5 alkylaminoC_1 –C_5 alkylamino or a heterocycle containing 4-8 ring atoms where one more of the ring atoms is nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with C_1 –C_5 alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substitutents are one or more of C_1 –C_5 alkyl, halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro), or R^{161} is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or

R^{161} is NR^{163} R^{164} where R^{163} and R^{164} are independently selected from hydrogen and $C_{1\text{-}5}$ alkyl or R^{163} and R^{164} may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C_1 –C_5 alkyl; R^{162} is hydrogen, C_1 –C_5 alkyl, nitro, amino, and halogen;

and pharmaceutically acceptable salts thereof.

[000134] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-substituted imidazoles that are described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula **XXXII**:



XXXII

wherein:

R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

substituted phenyl;

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

substituted heteroaryl;

wherein the substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl and halogen, or

substituted phenyl,

wherein the substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{166} is hydrogen, 2-(trimethylsilyl)ethoxymethyl), C_1 –C_5 alkoxycarbonyl, aryloxycarbonyl, arylC_1 –C_5 alkyloxycarbonyl, arylC_1 –C_5 alkyl, phthalimidoC_1 –C_5 alkyl, aminoC_1 –C_5 alkyl, diaminoC_1 –C_5 alkyl, succinimidoC_1 –C_5 alkyl, C_1 –C_5 alkylcarbonyl, arylcarbonyl, C_1 –C_5 alkylcarbonylC_1 –C_5 alkyl, aryloxycarbonylC_1 –C_5 alkyl, heteroarylC_1 –C_5 alkyl where the heteroaryl contains 5 to 6 ring atoms, or

substituted arylC_1 –C_5 alkyl,

wherein the aryl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, C_1 –C_5 alkoxy, halogen, amino, C_1 –C_5 alkylamino, and diC_1 –C_5 alkylamino;

R^{167} is $(A^{11})_n$–$(CH^{165})_q$–X^{24} wherein:

A^{11} is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X^{24} is selected from the group consisting of hydrogen, hydroxyl, halogen, vinyl, ethynyl, C_1 –C_5 alkyl, C_3 –C_7 cycloalkyl, C_1 –C_5 alkoxy, phenoxy, phenyl, arylC_1 –C_5 alkyl, amino, C_1 –C_5 alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylthio, C_1 –C_5 alkylsulfonyl, phenylsulfonyl,

substituted sulfonamido,

wherein the sulfonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, araC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted ethynyl,

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine chlorine and iodine,

substituted C_1 –C_5 alkyl,

wherein the substituents are selected from the group consisting of one or more C_1 –C_5 alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted phenoxy,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted C_1 –C_5 alkoxy,

wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,

substituted arylC_1 –C_5 alkyl,

wherein the alkyl substituent is hydroxyl,

substituted arylC_1 –C_5 alkyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted amido,

wherein the carbonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, arylC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl,

substituted phenylcarbonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted C_1 –C_5 alkylthio,

wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,

substituted C_1 –C_5 alkylsulfonyl,

wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,

substituted phenylsulfonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C_1 –C_5 alkoxy and trifluoromethyl,

with the proviso:

if A^{11} is sulfur and X^{24} is other than hydrogen, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

if A^{11} is sulfur and q is 1, then X^{24} cannot be C_1 –C_2 alkyl;

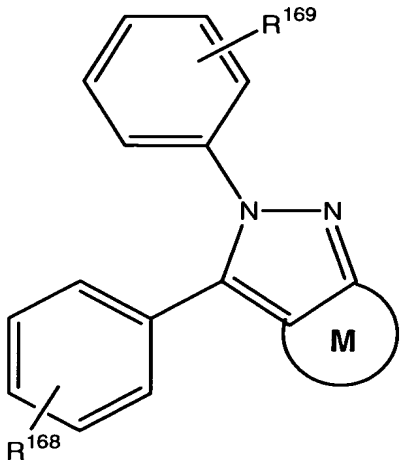
if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl;

if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not 2-(trimethylsilyl)ethoxymethyl;

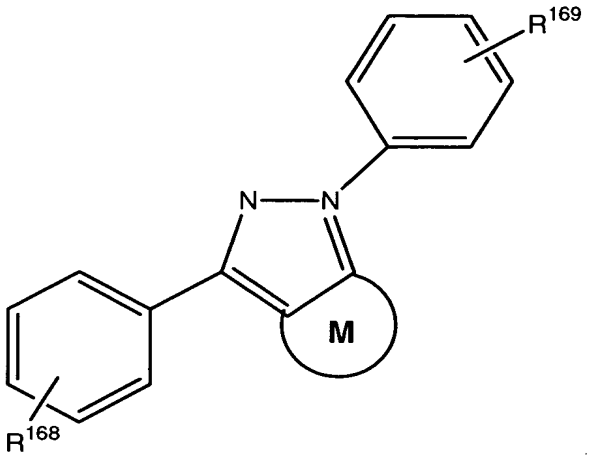
if n is 0 and q is 0, then X^{24} cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

[000135] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas **XXXIII** and **XXXIV**:



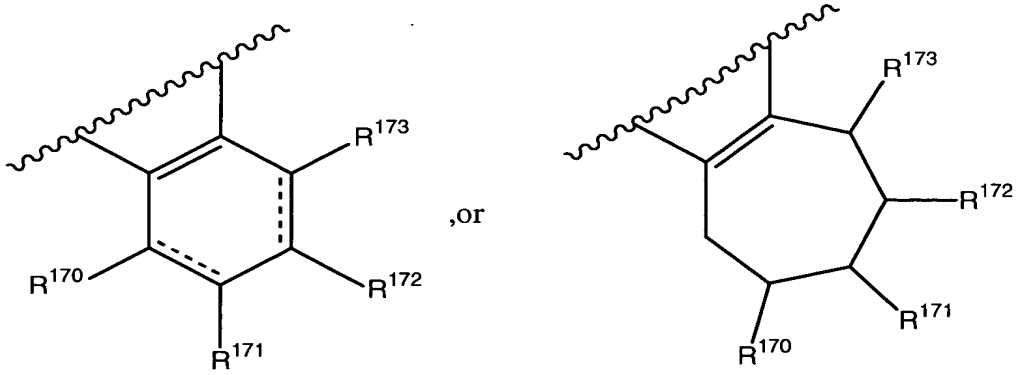
XXXIII



XXXIV

wherein:

R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy, nitro, amino, hydroxyl, trifluoro, —S(C_1 –C_6)alkyl, —SO(C_1 –C_6)alkyl and —SO_2 (C_1 –C_6)alkyl; and the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



wherein:

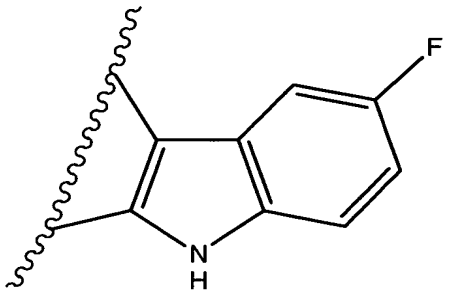
R^{170} is selected from the group consisting of hydrogen, halogen, hydroxyl and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of —$OCOCH_2$ —, —$ONH(CH_3)COCH_2$ —, —OCOCH= and —O—;

R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 – C_6)alkoxy, =NOH, —NR^{174} R^{175}, —OCH_3, —OCH_2 CH_3, —OSO_2 $NHCO_2$ CH_3, =$CHCO_2$ CH_2 CH_3, —CH_2 CO_2 H, —CH_2 CO_2 CH_3, —CH_2 CO_2 CH_2 CH_3, —CH_2 $CON(CH_3)_2$, —CH_2 CO_2 $NHCH_3$, —$CHCHCO_2$ CH_2 CH_3, —$OCON(CH_3)OH$, —$C(COCH_3)_2$, di(C_1 –C_6)alkyl and di(C_1 –C_6)alkoxy;

R^{173} is selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxyl, amino, (C_1 –C_6)alkyl and (C_1 –C_6)alkoxy;

or R^{172} and R^{173} taken together form a moiety selected from the group consisting of —O—and



R^{174} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$ and (C_1 –C_6)alkyl; and

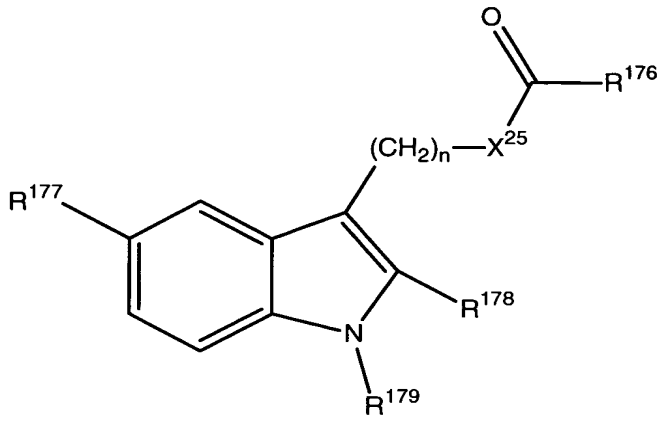
R^{175} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$, (C_1 –C_6)alkyl, —$CONH_2$ and —SO_2 CH_3 ;

with the proviso that if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

pharmaceutically acceptable salts, esters and pro-drug forms thereof.

[000136] Esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890

can serve as Cox-2 selective inhibitors of the present invention. Such compounds have the general formula shown below in formula **XXXV**:



XXXV

wherein:

R^{176} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_1 – C_6 hydroxyalkyl, branched C_1 –C_6 hydroxyalkyl, hydroxyl substituted C_4 – C_8 aryl, primary, secondary or tertiary C_1 –C_6 alkylamino, primary, secondary or tertiary branched C_1 –C_6 alkylamino, primary, secondary or tertiary C_4 –C_8 arylamino, C_1 –C_6 alkylcarboxylic acid, branched C_1 –C_6 alkylcarboxylic acid, C_1 –C_6 alkylester, branched C_1 –C_6 alkylester, C_4 –C_8 aryl, C_4 –C_8 arylcarboxylic acid, C_4 –C_8 arylester, C_4 –C_8 aryl substituted C_1 –C_6 alkyl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R^{177} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_4 – C_8 aryl, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, C_1 –C_6 branched alkoxy, C_4 –C_8 aryloxy, or halo-substituted versions thereof or R^{177} is halo where halo is chloro, fluoro, bromo, or iodo;

R^{178} is hydrogen, C_1 –C_6 alkyl or C_1 –C_6 branched alkyl;

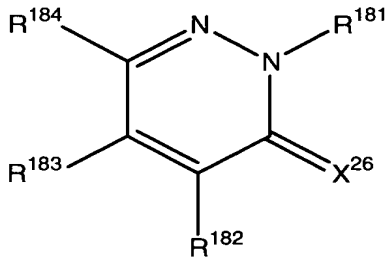
R^{179} is C_1 –C_6 alkyl, C_4 –C_8 aroyl, C_4 –C_8 aryl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O,

N or S in the ring, alkyl-substituted C_4 –C_8 aroyl, or alkyl-substituted C_4 – C_8 aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

n is 1, 2, 3, or 4; and

X^{25} is O, NH, or N—R^{180}, where R^{180} is C_1 –C_6 or C_1 –C_6 branched alkyl.

[000137] Materials that can serve as a Cox-2 selective inhibitor of the present invention include pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula **XXXVI**:



XXXVI

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

X^{26} is selected from the group consisting of O, S, —NR^{185}, —NOR^a, and –NNR^b R^c ;

R^{185} is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

R^a, R^b, and R^c are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

R^{181} is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic

alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, —$(CH_2)_n$ $C(O)R^{186}$, —$(CH_2)_n$ $CH(OH)R^{186}$, —$(CH_2)_n$ $C(NOR^d)R^{186}$, —$(CH_2)_n$ $CH(NOR^d)R^{186}$, —$(CH_2)_n$ $CH(NR^d\ R^e)R^{186}$, —R^{187} R^{188}, —$(CH_2)_n$ $C{\equiv}CR^{188}$, —$(CH_2)_n$ $[CH(CX^{26'}{}_3)]_m$ $(CH_2)_p$ R^{188}, —$(CH_2)_n$ $(CX^{26'}{}_2)_m$ $(CH_2)_p$ R^{188}, and —$(CH_2)_n$ $(CHX^{26'})_m$ $(CH_2)_m$ R^{188} ;

R^{186} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;

R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

$X^{26'}$ is halogen;

m is an integer from 0-5;

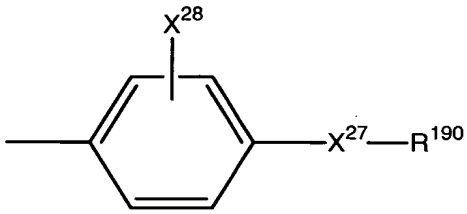
n is an integer from 0-10;

p is an integer from 0-10;

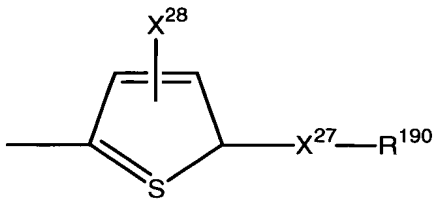
R^{182}, R^{183}, and R^{184} are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y^8, and Z^{14};

provided that one of R^{182}, R^{183}, or R^{184} must be Z^{14}, and further provided that only one of R^{182}, R^{183}, or R^{184} is Z^{14};

Z^{14} is selected from the group consisting of:



and



X^{27} is selected from the group consisting of $S(O)_2$, $S(O)(NR^{191})$, S(O), $Se(O)_2$, $P(O)(OR^{192})$, and $P(O)(NR^{193}\ R^{194})$;

X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, —$NHNH_2$, and —$NCHN(R^{191})R^{192}$;

R^{191}, R^{192}, R^{193}, and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188} ;

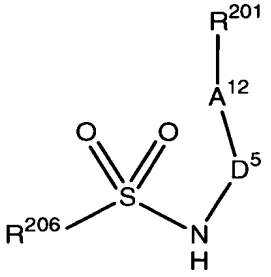
Y^8 is selected from the group consisting of $-OR^{195}$, —SR^{195}, —$C(R^{197})(R^{198})R^{195}$, —$C(O)R^{195}$, —$C(O)OR^{195}$, —$N(R^{197})C(O)R^{195}$, —$NC(R^{197})R^{195}$, and —$N(R^{197})R^{195}$;

R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and $NR^{199}\ R^{200}$; and

R^{197}, R^{198}, R^{199}, and R^{200} are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

[000138] Benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948 are useful as Cox-2 selective inhibitors of the

present invention. Such benzosulphonamide derivatives have the formula shown below in formula **XXXVII**:



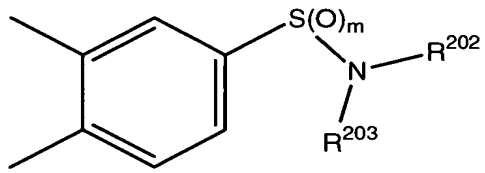
XXXVII

wherein:

A^{12} denotes oxygen, sulphur or NH;

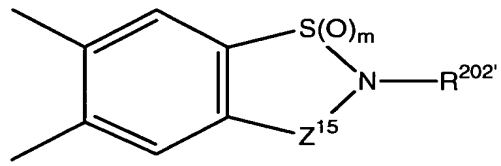
R^{201} denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF_3 or alkoxy;

D^5 denotes a group of formula **XXXVIII** or **XXXIX**:



XXXVIII

or



XXXIX

R^{202} and R^{203} independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical $(CH_2)_n -X^{29}$; or

R^{202} and R^{203} together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n -X^{29}$, $R^{202'}$ denotes

hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n -X^{29}$,

wherein:

X^{29} denotes halogen, NO_2, $—OR^{204}$, $—COR^{204}$, $—CO_2 R^{204}$, $—OCO_2 R^{204}$, —CN, $—CONR^{204} OR^{205}$, $—CONR^{204} R^{205}$, $—SR^{204}$, $—S(O)R^{204}$, $—S(O)_2 R^{204}$, $—NR^{204} R^{205}$, $—NHC(O)R^{204}$, $—NHS(O)_2 R^{204}$;

Z^{15} denotes $–CH_2 —$, $—CH_2 –CH_2 —$, $—CH_2 –CH_2 –CH_2 —$, $—CH_2 –CH=CH—$, $—CH=CH—CH_2 —$, $—CH_2 —CO—$, $—CO—CH_2 —$, —NHCO—, —CONH—, $—NHCH_2 —$, $—CH_2 NH—$, —N=CH—, —NHCH—, $—CH_2–CH_2—NH—$, —CH=CH—, $>N—R^{203}$, >C=O, $>S(O)_m$;

R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

n is an integer from 0 to 6;

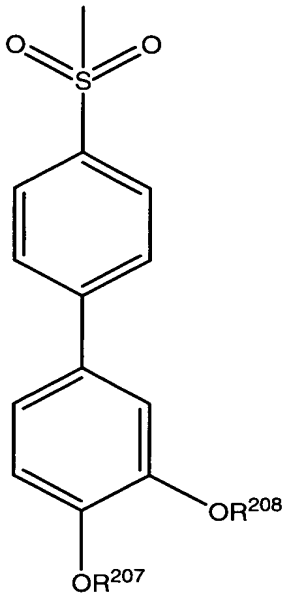
R^{206} is a straight-chained or branched $C_1 –C_4$ alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3; and

m denotes an integer from 0 to 2;

with the proviso that A^{12} does not represent O if R^{206} denotes CF_3;

and the pharmaceutically acceptable salts thereof.

[000139] Materials that can serve as Cox-2 selective inhibitors of the present invention include methanesulfonyl-biphenyl derivatives that are described in U.S. Patent No. 6,583,321. Such methanesulfonyl-biphenyl derivatives have the formula shown below in formula **XL**:



XL

wherein:

R^{207} and R^{208} are respectively a hydrogen;

C_1 –C_4-alkyl substituted or not substituted by halogens;

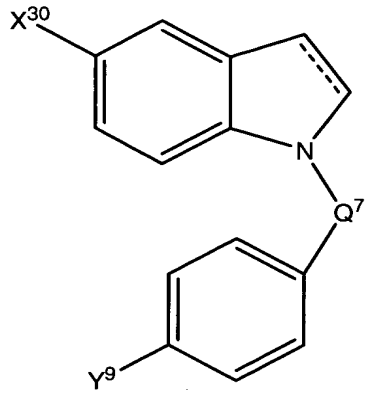
C_3 –C_7-cycloalkyl;

C_1 –C_5-alkyl containing 1-3 ether bonds and/or an aryl substitute;

substituted or not substituted phenyl;

or substituted or not substituted five or six ring-cycled heteroaryl containing more than one hetero atoms selected from a group consisting of nitrogen, sulfur, and oxygen (wherein phenyl or heteroaryl can be one- or multi-substituted by a substituent selected from a group consisting of hydrogen, methyl, ethyl, and isopropyl).

[000140] Cox-2 selective inhibitors such as 1H-indole derivatives described in U.S. Patent No. 6,599,929 are useful in the present invention. Such 1H-indole derivatives have the formula shown below in formula **XLI**:



XLI

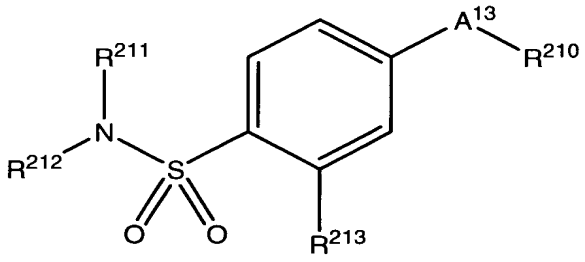
wherein:

X^{30} is $-NHSO_2R^{209}$ wherein R^{209} represents hydrogen or C_1 $-C_3-$ alkyl;

Y^9 is hydrogen, halogen, C_1 $-C_3-$alkyl substituted or not substituted by halogen, NO_2, NH_2, OH, OMe, CO_2H, or CN; and

Q^7 is C=O, C=S, or CH_2.

[000141] Compounds that are useful as Cox-2 selective inhibitors of the present invention include prodrugs of Cox-2 inhibitors that are described in U.S. Patent Nos. 6,436,967 and 6,613,790. Such prodrugs of Cox-2 inhibitors have the formula shown below in formula **XLII**:



XLII

wherein:

A^{13} is a ring substituent selected from partially unsaturated heterocyclic, heteroaryl, cycloalkenyl and aryl, wherein A^{13} is unsubstituted or substituted with one or more radicals selected from alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulfonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl,

cycloalkylalkyl, alkenyl, alkynyl, heterocycloxy, alkylthio, cycloalkyl, aryl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, araalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, -arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl;

R^{210} is selected from heterocyclyl, cycloalkyl, cycloalkenyl, and aryl, wherein R^{210} is unsubstituted or substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} is selected from hydrido and alkoxycarbonylalkyl;

R^{212} is selected from alkyl, carboxyalkyl, acyl, alkoxycarbonyl, heteroarylcarbonyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylcarbonyl, amino acid residue, and alkylcarbonylaminoalkylcarbonyl;

provided A^{13} is not tetrazolium, or pyridinium; and further provided A^{13} is not indanone when R^{212} is alkyl or carboxyalkyl; further provided A^{13} is not thienyl, when R^{210} is 4-fluorophenyl, when R^{211} is hydrido, and when R^{212} is methyl or acyl; and

R^{213} is hydrido;

or a pharmaceutically-acceptable salt thereof.

[000142] Specific non-limiting examples of substituted sulfonamide prodrugs of Cox-2 inhibitors disclosed in U.S. Patent No. 6,436,967 that are useful in the present invention include:

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]propanamide;

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phen yl]sulfonyl]butanamide;
N-[[4-[1,5-dimethyl)-3-phenyl-1H-pyrazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(3-chloro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(3-fluorophenyl)-5-methylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
2-methyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]benzamide;
2,2-dimethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]pentanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]hexanamide;
3-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide ;
2-ethoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H pyrazol-1-yl]phenyl]sulfonyl]propanamide;

N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-6-fluoro-1,5-dihydro-7-methoxy-[2]benzothiopyrano [4,3-c]pyrazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[6-fluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-methyl-4-phenyloxazol-5-yl)phenyl]sulfonyl]acetamide;
methyl[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]oxoacetate;
2-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]formamide;
1,1-dimethylethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-[[.sup.4 -(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine;
2-amino-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
2-(acetylamino)-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
methyl 4-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-4-oxobutanoate;
methyl N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-acetyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine, ethyl ester;
N-[[4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl]sulfonyl]acetamide;

methyl 3-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-3-oxopropanoate;
4-[5-(3-bromo-5-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)oxazol-4-yl]-N-methylbenezenesulfonamide;
N-(1,1-dimethylethyl)-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-methylbenzenesulfonamide;
N-methyl-4-(5-methyl-3-phenylisoxazol-4-yl)benezenesulfonamide;
N-[[4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide:
N-[[4-[5-(acetoxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl)phenyl]sulfonyl]acetamide;
4-[2-(4-fluorophenyl)-1H-pyrrol-1-yl]-N-methylbenzenesulfonamide;
N-[[4-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl]phenyl]sulfonyl]propanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-trifluoromethylimidazol-1-yl]phenyl]sulfonyl]propanamide;
4-[2-(4-fluorophenyl)cyclopenten-1-yl]-N-methylbenezenesulfonamide; and
N-[[4-(3-phenyl-2,3-dihydro-2-oxofuran-4-yl)phenyl]sulfonyl]propanamide.

[000143] Those prodrugs disclosed in U.S. Patent No. 6,613,790 have the general formula shown above in formula **XLII** wherein:

A^{13} is a pyrazole group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, intro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, alkenyl, alkynyl, alkylthio, alkylthioalkyl, alkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkylsutfinyl, alkylsulfonyl, aminosulfonyl, and alkylaminosulfonyl;

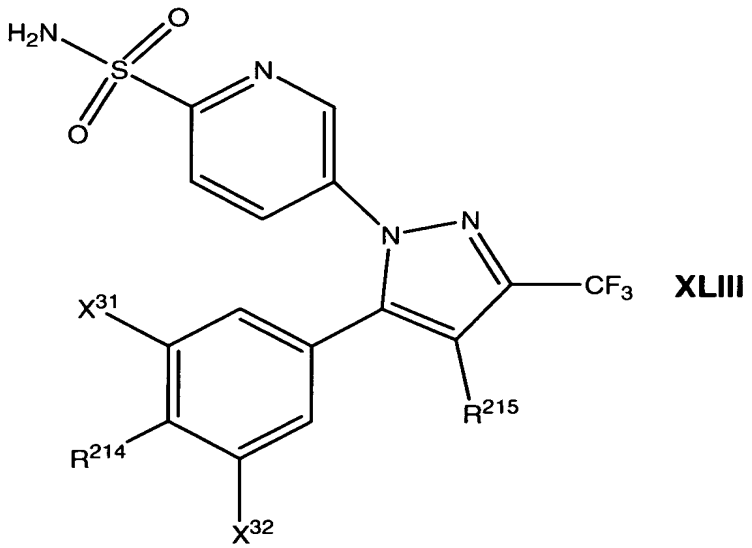
R^{210} is a phenyl group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} and R^{212} are independently selected from the group consisting of hydroxyalkyl and hydrido but at least one of R^{211} and R^{212} is other than hydrido; and

R^{213} is selected from the group consisting of hydrido and fluoro.

[000144] Examples of prodrug compounds disclosed in U.S. 6,613,790 that are useful as Cox-2 inhibitors of the present invention include, but are not limited to, N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1- yl]benzenesulfonamide, N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyraz ol-1-yl]benzenesulfonamide, or pharmaceuticaly-acceptable salts thereof.

[000145] Cox-2 selective inhibitors such as sulfamoylheleroaryl pyrazole compounds that are described in U.S. Patent No. 6,583,321 may serve as Cox-2 inhibitors of the present invention. Such sulfamoylheleroaryl pyrazole compounds have the formula shown below in formula **XLIII**:



XLIII

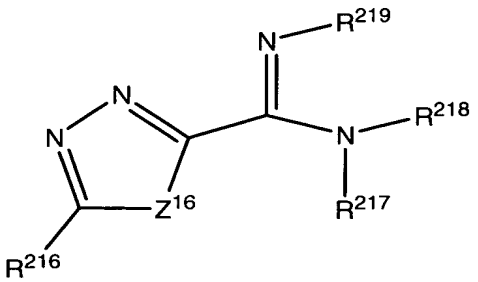
wherein:

R^{214} is furyl, thiazolyl or oxazolyl;

R^{215} is hydrogen, fluoro or ethyl; and

X^{31} and X^{32} are independently hydrogen or chloro.

[000146] Heteroaryl substituted amidinyl and imidazolyl compounds such as those described in U.S. Patent No. 6,555,563 are useful as Cox-2 selective inhibitors of the present invention. Such heteroaryl substituted amidinyl and imidazolyl compounds have the formula shown below in formula **XLIV**



XLIV

wherein:

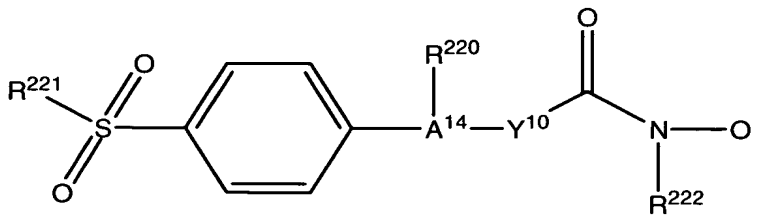
Z^{16} is O or S,

R^{216} is optionally substituted aryl,

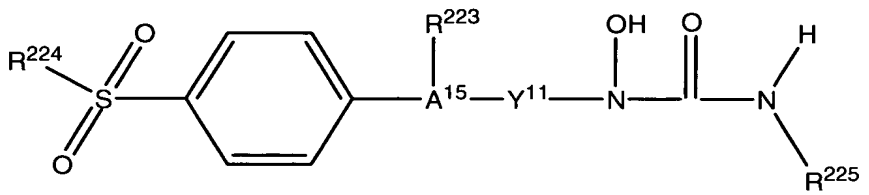
R^{217} is aryl optionally substituted with aminosulfonyl, and

R^{218} and R^{219} cooperate to form an optionally substituted 5-membered ring.

[000147] Materials that can serve as Cox-2 selective inhibitors of the present invention include substituted hydroxamic acid derivatives that are described in U.S. Patent Nos. 6,432,999, 6,512,121, and 6,515,014. These compounds also act as inhibitors of the lipoxygenase-5 enzyme. Such substituted hydroxamic acid derivatives have the general formulas shown below in formulas **XLV** and **XLVI**:



XLV



XLVI

[000148] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 have the formula shown above in formula **XLV**, wherein:

A^{14} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is selected from lower alkenylene and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000149] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 may also have the formula shown above in formula **XLVI**, wherein:

A^{15} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro,

carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkylene, lower alkenylene and lower alkynylene;

[000150] R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido, lower alkyl;

or a pharmaceutically-acceptable salt thereof.

[000151] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 have the formula shown above in formula **XLV**, wherein:

A^{14} is a ring substiuent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isochiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A^{14} is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is lower alkylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is otionallv substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino,

phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000152] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 may also have the formula shown above in formula **XLVI**, wherein:

A^{15} is a ring substituent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isothiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarboryl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitto, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000153] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 have the formula shown above in formula **XLV**, wherein:

A^{14} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl,

lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is ethylene, isopropylene, propylene, butylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000154] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 may also have the formula shown above in formula **XLV**, wherein:

A^{15} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

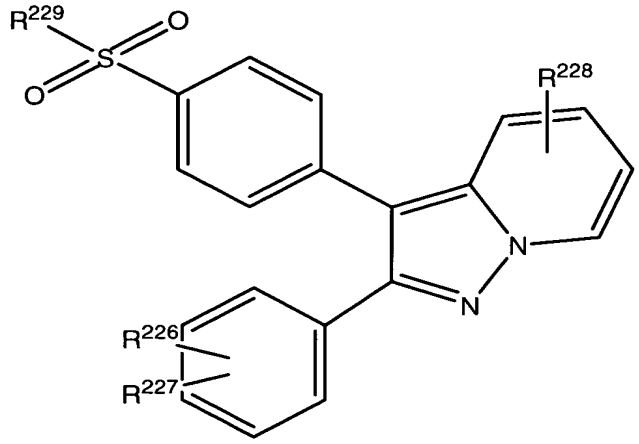
Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000155] Compounds that are useful as Cox-2 selective inhibitors of the present invention include pyrazolopyridine compounds that are described in U.S. Patent No. 6,498,166. Such pyrazolopyridine compounds have the formula shown below in formula **XLVII**:



XLVII

wherein:

R^{226} and R^{227} are independently selected from the group consisting of H, halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms;

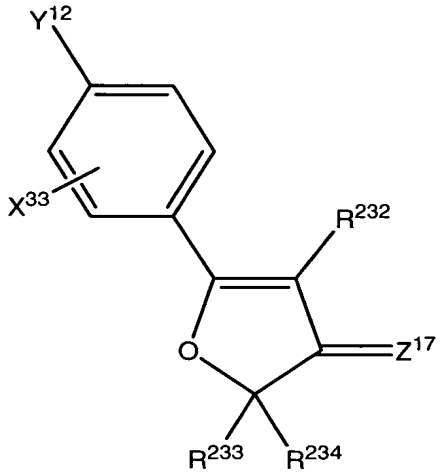
R^{228} is halogen, CN, CON R^{230} R^{231}, CO_2 H, CO_2 C_1 –C_6 alkyl, or $NHSO_2R^{230}$;

R^{229} is C_1 –C_6 alkyl or NH_2 ; and

R^{225} and R^{225} are independently selected from the group consisting of H, C_1 –C_6 alkyl, phenyl, phenyl substituted by one or more atoms or groups selected from the group consisting of halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms, or a pharmaceutically acceptable salt, solvate, ester, or salt or solvate of such ester thereof.

[000156] Materials that are useful as Cox-2 selective inhibitors of the present invention include 4,5-diaryl-3(2H)-furanone derivatives that are

described in U.S. Patent No. 6,492,416. Such 4,5-diaryl-3(2H)-furanone derivatives have the formula shown below in formula **XLVIII**:



XLVIII

wherein:

X^{33} represents halo, hydrido, or alkyl;

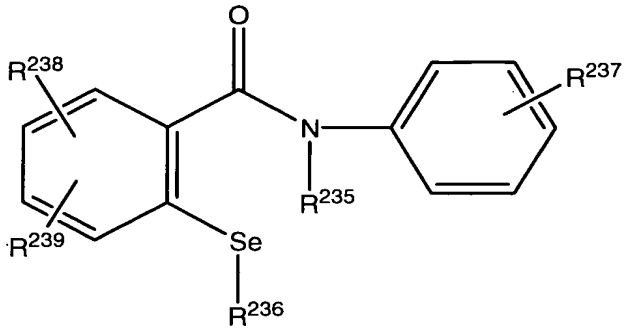
Y^{12} represents alkylsulfonyl, aminosulfonyl, alkylsulfinyl, (N-acylamino)-sulfonyl, (N-alkylamino)sulfonyl, or alkylthio;

Z^{17} represents oxygen or sulfur atom;

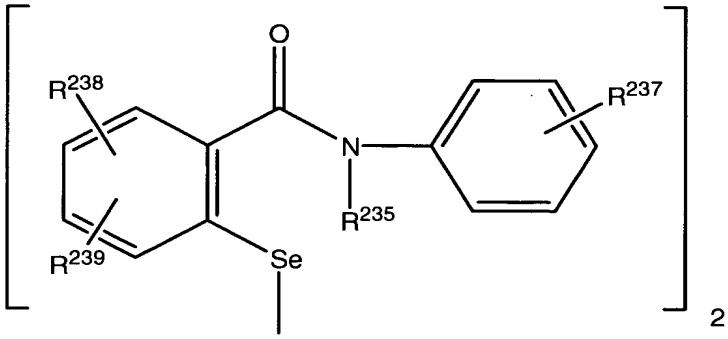
R^{233} and R^{234} are selected independently from lower alkyl radicals; and R^{232} represents a substituted or non-substituted aromatic group of 5 to 10 atoms;

or a pharmaceutically-acceptable salt thereof.

[000157] Cox-2 selective inhibitors that can be used in the present invention include 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives that are described in U.S. Patent No. 6,492,416. Such 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives have the formulas shown below in formulas **XLIX** or **XLIX'**:



XLIX



XLIX'

wherein:

R^{235} is a hydrogen atom or an alkyl group having 1-3 carbon atoms;

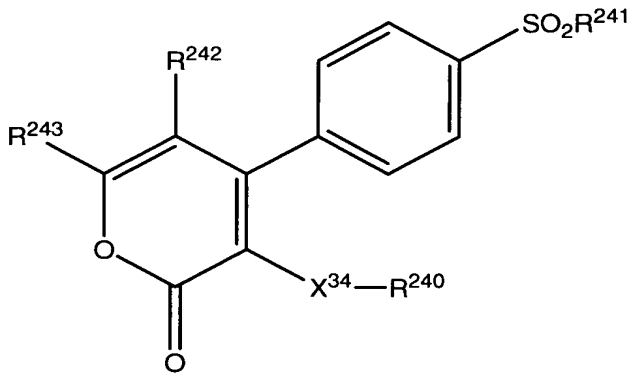
R^{236} is a hydrogen atom, a hydroxyl group, an organothiol group that is bound to the selenium atom by its sulfur atom, or R^{235} and R^{236} are joined to each other by a single bond;

R^{237} is a hydrogen atom, a halogen atom, an alkyl group having 1-3 carbon atoms, an alkoxyl group having 1-3 carbon atoms, a trifluoromethyl group, or a nitro group;

R^{238} and R^{239} are identical to or different from each other, and each is a hydrogen atom, a halogen atom, an alkoxyl group having 1-4 carbon atoms, a trifluoromethyl group, or R^{238} and R^{239} are joined to each other to form a methylenedioxy group,

a salt thereof, or a hydrate thereof.

[000158] Pyrones such as those disclosed in U.S. Patent No. 6,465,509 are also useful as Cox-2 inhibitors of the present invention. These pyrone compounds have the general formula shown below in formula **L:**



L

wherein:

X^{34} is selected from the group consisting of:

(a) a bond,

(b) --$(CH_2)_m$ --, wherein m 1 or 2,

(c) --C(O)--,

(d) --O--,

(e) --S--, and

(f) --$N(R^{244})$--;

R^{240} is selected from the group consisting of:

(a) C_1 –C_{10} alkyl, optionally substituted with 1-3 substituents independently selected from the group consisting of: hydroxy, halo, C_1 –C_{10} alkoxy, C_1 – C_{10} alkylthio, and CN,

(b) phenyl or naphthyl, and

(c) heteroaryl, which is comprised of a monocyclic aromatic ring of 5 atoms having one hetero atom which is S, O or N, and optionally 1, 2, or 3 additional N atoms; or

a monocyclic ring of 6 atoms having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein groups (b) and (c) above are each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, C_1 –C_{10} alkoxy, C_1 –C_{10} alkylthio, CN, C_1 –C_{10} alkyl, optionally substituted to its maximum with halo, and N_3 ;

R^{241} is selected from the group consisting of

(a) C_1 –C_6 alkyl, optionally substituted to its maximum with halo,

(b) NH_2, and

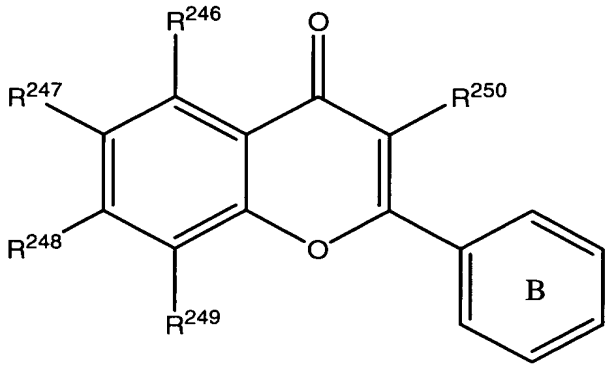
(c) $NHC(O)C_1$ –C_{10} alkyl, optionally substituted to its maximum with halo;

R^{242} and R^{243} are each independently selected from the group consisting of: hydrogen, halo, and C_1 –C_6 alkyl, optionally substituted to its maximum with halo; and

R^{244} is selected from the group consisting of: hydrogen and C_1 –C_6 alkyl, optionally substituted to its maximum with halo.

[000159] Examples of pyrone compounds that are useful as Cox-2 selective inhibitors of the present invention include, but are not limited to:
4-(4-Methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
3-(4-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
3-(3-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Difluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Fluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenylthio-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenoxy-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-pyridin-3-yl-pyran-2-one,
3-Isopropylthio-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl)-3-phenylthio-6-trifluoromethyl-pyran-2-one,
3-Isopropylthio-4-(4-methylsulfonyl)phenyl-6-trifluoromethyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl-3-phenyl-6-(2,2,2-trifluoroethyl)-pyran-2-one, and
3-(3-Hydroxy-3-methylbutyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one.

[000160] Organically synthesized or purified from plant sources, free-B-ring flavanoids such as those described in U.S. Published Application No. 2003/0165588, are useful as Cox-2 selective inhibitors of the present invention. Such free-B-ring flavanoids have the general structure shown in formula **LI**:

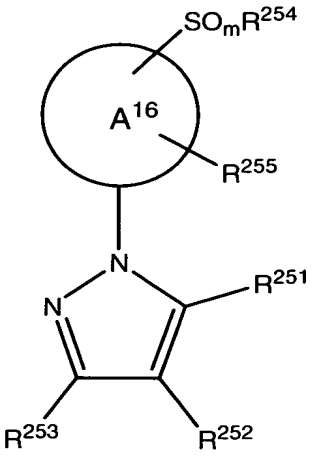


LI

wherein:

R^{246}, R^{247}, R^{248}, R^{249}, and R^{250} are independently selected from the group consisting of: --H, --OH, --SH, --OR, --SR, --NH_2, --NHR^{245}, --$N(R^{245})_2$, --$N(R^{245})_3{}^+X^{35-}$, a carbon, oxygen, nitrogen or sulfur, glycoside of a single or a combination of multiple sugars including, aldopentoses, methyl-aldopentose, aldohexoses, ketohexose and their chemical derivatives thereof; wherein R^{245} is an alkyl group having between 1-10 carbon atoms; and X^{35} is selected from the group of pharmaceutically acceptable counter anions including, hydroxyl, chloride, iodide, sulfate, phosphate, acetate, fluoride and carbonate.

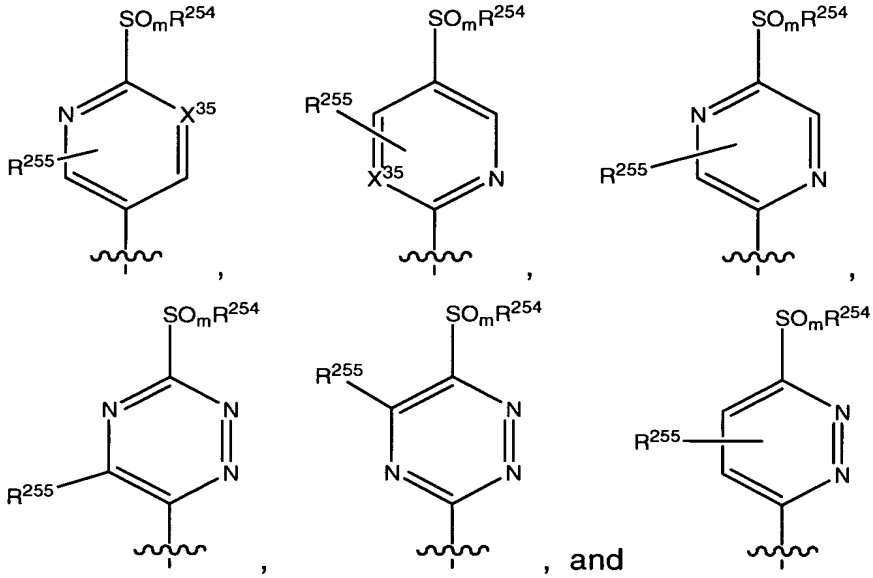
[000161] Heterocyclo-alkylsulfonyl pyrazoles such as those described in European Patent Application No. EP 1312367 are useful as Cox-2 selective inhibitors of the present invention. Such heterocyclo-alkylsulfonyl pyrazoles have the general formula shown below in formula **LII**:



LII

or a pharmaceutically acceptable salt thereof, wherein:

the ring of the formula (R^{255})-A-(SO_mR^{254}) is selected from the group consisting of:



; m is 0, 1 or 2;

X^{35} is $>CR^{255}$ or >N;

R^{251} is a radical selected from the group consisting of H, NO_2, CN, (C_1-C_6)alkyl, (C_1-C_6)alkyl-SO_2-, (C_6-C_{10})aryl-SO_2-, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_1-C_6)alkyl-)-(C=O)-, (C_1-C_9)heteroaryl-(C=O)-, (C_1-C_9)heterocyclyl-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, $[(C_1-C_6)alkyl]_2$-N-(C=O)-, $[(C_6-C_{10})aryl]_2$-NH-(C=O)-, $[(C_1-C_6)alkyl]$-[$((C_6-C_{10})aryl-N]$-(C=O)-, HO-NH-(C=O)-, and (C_1-C_6)alkyl-O-NH-(C=O)-;

R^{252} is a radical selected from the group consisting of H, -NO_2, -CN, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_1-C_9)heteroaryl, (C_1-C_9)heterocyclyl, (C_1-C_6)alkyl-O-, (C_3-C_7)cycloalkyl-O-, (C_6-C_{10})aryl-O-, (C_1-C_9)heteroaryl-O-, (C_6-C_9)heterocyclyl-O-, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_3-C_7)cycloalkyl-(C=O)-, (C_6-C_{10})aryl-(C=O)-, (C_1-C_9)heteroaryl-(C=O)-, (C_1-C_9)heterocyclyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_7)cycloalkyl-O-(C=O)-, (C_6-C_{10})aryl-O-(C=O)-, (C_1-C_9)heteroaryl-O-(C=O)-, (C_1-C_9)heterocyclyl-O-(C=O)-, (C_1-C_6)alkyl-(C=O)-O-, (C_3-C_7)cycloalkyl-(C=O)-O-, (C_6-C_{10})aryl-(C=O)-O-, (C_1-C_9)heteroaryl-(C=O)-

O-, (C_1-C_9)heterocyclyl-(C=O)-O-, (C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_7)cycloalkyl-(C=0)-NH-, (C_6-C_{10}aryl-(C=O)-NH-. (C_1-C_9)heteroaryl-(C=O)-NH-, (C_1-C_9)heterocyclyl-(C=O)-NH-, (C_1-C_6)alkyl-O-(C=O)-NH-, (C_1-C_6)alkyl-NH, [(C_1-C_6)alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-. [(C_3-C_7)cycloalkyl]$_2$-N-, [(C_6-C_{10})aryl]-NH-, [(C_6-C_{10})aryl]$_2$-N-, [(C_1 –C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, [(C_1 -C_9)heteroaryl]-NH-, [(C_1-C_9)heteroaryl]$_2$-N-, [(C_1-C_9)heterocycly]-NH-, [(C_1-C_9)heterocyclyl]$_2$-N-, H_2N-(C=O)-, HO-NH-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, [(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_3-C_7)cycloalkyl]-NH-(C=O)-, [(C_3-C_7)cycloalkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_6-C_{10}aryl]$_2$-N-(C=O)-, [(C_1-C $_6$)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, [(C_1-C_9)heteroaryl]-NH-(C=O)-, [(C_1-C_9)heferoaryl]$_2$-N-(O=O)-, [(C_1-C_9)heterocyclyl]-NH-(C=O)-, (C_1–C_6)alkyl-S- and (C_1-C_6)alkyl optionally substituted by one -OH substituent or by one to four fluoro substituents;

R^{253} is a saturated (3- to 4-membered)-heterocyclyl ring radical; or a saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical orsaid saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may optionally contain one to four ring heteroatoms independently selected Irom the groups consisting of -N=, -NH-, -O-. and -S-;

wherein said saturated (3- to 4-membered)-heterooycyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-nembered)-heterocyclyl ring radical; may optionally be substituted on any ring carbon atom by one to three substituents per ring independently selected from the group consisting of halo, -OH, -CN, -NO_2, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)hetorocyclyl, (C_1 –C_6)alkyl-O-, H-(C=0)-, (C_1-C_6)alkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, -NH_2, (C_1-C_6)alkyl-NH-, [(C_1-C_6) alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-, (C_6-C_{10})aryl-NH-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, (C_1-C_9)heteroaryl-NH-, H_2N-(C=O)-[(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-

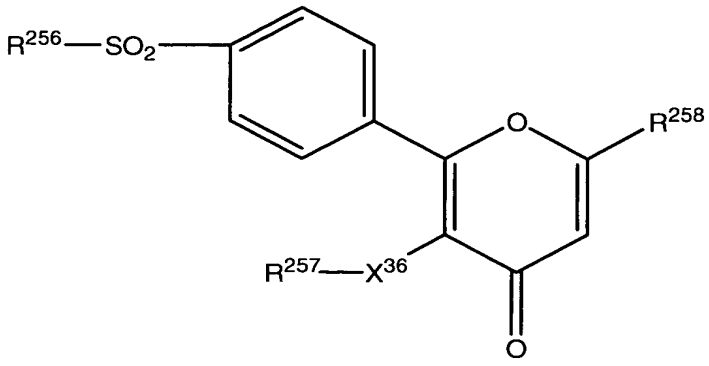
N]-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-HN-, (C_1-C_6)alkyl-(C=O)-[(C_1-C_6)alkyl-N]-, -SH, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-(S=0)-, (C_1-C_6)alkyl-SO_2- and (C_1-C_6)alkyl optionally substituted with one to fourfluoro moieties;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may also optionally be substituted on any ring nitrogen atom by one to three substituents per ring independently selected from the group consisting of (C_3-C_7)cyoloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, [(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, (C_1 –C_6)alkyl-O-NH-(C=O)-, and (C_1-C_6)alkyl optionally substituted with one to four fluoro moieties;

R^{254} is an (C_1-C_6)alkyl radical optionally substituted by one to four fluoro substituents; and

R^{255} is a radical selected from the group consisting of H, halo, -OH, (C_1-C_6)alkyl-O-, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, (C_3-C_7)cycloalkyl, -CN, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_1-C_6)alkyl-(C=O)-O-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_1-C_6)alkyl-NH-. [(C_1-C_6)alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-, (C_6-C_{10})aryl-NH-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, (C_1-C_9)heteroaryl-NH-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-. [(C_1-C_6)alkyl]$_2$-N-(C=O)-, (C_6-C_{10})aryl-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, (C_1-C_6)alkyl-S-, and (C_1-C_6)alkyl optionally substituted by one to four fluoro substituents.

[000162] 2-phenylpyran-4-one derivatives such as those described in U.S. Patent No. 6,518,303 are also useful as Cox-2 selective inhibitors of the present invention. Such 2-phenylpyran-4-one derivatives have the general formula shown below in formula **LIII**:



LIII

wherein:

R^{256} represents an alkyl or $-NR^{259}$ R^{260} group, wherein R^{259} and R^{260} each independently represents a hydrogen atom or an alkyl group;

R^{257} represents an alkyl, C_3 –C_7 cycloalkyl, naphthyl, tetrahydronaphthyl or indanyl group, or a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

R^{258} represents a methyl, hydroxymethyl, alkoxymethyl, C_3 –C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a CH_2 -- R^{261} group wherein R^{261} represents an alkyl group; and X^{36} represents a single bond, an oxygen atom, a sulfur atom or a methylene group;

or a pharmaceutically acceptable salt thereof.

[000163] Examples of 2-phenylpyran-4-one derivatives useful in the present invention include, but are not limited to:

3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenyl)-2-(4-methylsulfonylphenyl)-6-methylpyran-4-one,
3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one ,

2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxypyran-4-one,
3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methylphenoxy)pyran-4-one,
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one,
3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonylphenyl)pyran-4-one,
and pharmaceutically acceptable salts thereof.

[000164] Cox-2 selective inhibitors that are useful in the subject method and compositions can also include the compounds that are described in U.S. Patent No. 6,472,416 (sulfonylphenylpyrazoles); U.S. Patent No. 6,451,794 (2,3-diaryl-pyrazolo[1,5-b]pyridazines); U.S. Patent Nos. 6,169,188, 6,020,343, and 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); U.S. Patent Nos. 6,359,182 and 6,538,116 (C-nitroso compounds); U.S. Published Application No. 2003/0065011 (substituted pyridines); U.S. Published Application No. 2003/0207897 (substituted indole derivatives); and mixtures thereof.

[000165] Examples of specific compounds that are useful as Cox-2 selective inhibitors include, without limitation:

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h9) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

[000166] Cox-2 inhibitors that are useful in the methods and compositions of present invention can be supplied by any source as long as the Cox-2 inhibitor is pharmaceutically acceptable. Likewise, Cox-2 inhibitors that are useful in the compositions and methods of present invention can be synthesized, for example, according to the description in Example 1. Several Cox-2 inhibitors that are suitable for use with the compositions and methods of the present invention may be synthesized by the methods described in, for example, in U.S. Patent No. 5,466,823 to Talley, *et al.*

[000167] Preferred Cox-2 selective inhibitor compounds are those compounds selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib, RS 57067, T-614, BMS-347070 (Bristol Meyers Squibb, described in U.S. Patent No. 6,180,651), JTE-522 (Japan Tabacco), S-2474 (Shionogi), SVT-2016, CT-3 (Atlantic Pharmaceutical), ABT-963 (Abbott), SC-58125 (GD Searle), nimesulide, flosulide, NS-398 (Taisho Pharmaceutical), L-745337 (Merck), RWJ-63556, L-784512 (Merck), darbufelone (Pfizer), CS-502 (Sankyo), LAS-34475 (Almirall Prodesfarma), LAS-34555 (Almirall Prodesfarma), S-33516 (Servier), SD-8381 (Pharmacia, described in U.S. Patent No. 6,0340256), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1376 (Chiroscience), L-748731 (Merck), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), prodrugs of any of them, and mixtures thereof.

[000168] More preferred is that the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

[000169] Even more preferred still is that the Cox-2 selective inhibitor is celecoxib.

[000170] Cox-2 inhibitors that are useful in the methods and compositions and methods of present invention can be supplied by any source as long as the Cox-2 inhibitor is pharmaceutically acceptable.

[000171] Various classes of Cox-2 inhibitors useful in the present invention can be prepared as follows. Pyrazoles can be prepared by methods described in WO 95/15316. Pyrazoles can further be prepared by methods described in WO 95/15315. Pyrazoles can also be prepared by methods described in WO 96/03385.

[000172] Thiophene analogs useful in the present invention can be prepared by methods described in WO 95/00501. Preparation of thiophene analogs is also described in WO 94/15932.

[000173] Oxazoles useful in the present invention can be prepared by the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980.

[000174] Isoxazoles useful in the present invention can be prepared by the methods described in WO 96/25405.

[000175] Imidazoles useful in the present invention can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387.

[000176] Cyclopentene Cox-2 inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentene Cox-2 inhibitors is also described in WO 95/00501.

[000177] Terphenyl compounds useful in the present invention can be prepared by the methods described in WO 96/16934.

[000178] Thiazole compounds useful in the present invention can be prepared by the methods described in WO 96/03,392.

[000179] Pyridine compounds useful in the present invention can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24,585.

[000180] Benzopyranopyrazolyl compounds useful in the present invention can be prepared by the methods described in WO 96/09304.

[000181] Chromene compounds useful in the present invention can be prepared by the methods described in WO 98/47890. Preparation of chromene compounds is also described in WO 00/23433. Chromene

compounds can further be prepared by the methods described in U.S. Patent No. 6,077,850. Preparation of chromene compounds is further described in U.S. Patent No. 6,034,256.

[000182] Arylpyridazinones useful in the present invention can be prepared by the methods described in WO 00/24719. Preparation of arylpyridazinones is also described in WO 99/10332. Arylpyridazinones can further be prepared by the methods described in WO 99/10331.

[000183] 5-Alkyl-2-arylaminophenylacetic acids and derivatives useful in the present invention can be prepared by the methods described in WO 99/11605.

[000184] Diarylmethylidenefuran derivative Cox-2 selective inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 6,180,651.

[000185] The celecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

[000186] The valdecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

[000187] The parecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

[000188] The rofecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,474,995.

[000189] The deracoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,521,207.

[000190] The etoricoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 98/03484.

[000191] The meloxicam used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,233,299.

[000192] The compound 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,994,381.

[000193] The compound 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 00/24719.

[000194] The compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one used in the compositions and methods of the present invention can be prepared in the manner set forth in EP 863134.

[000195] The compound 2-[(2-chloro-6-fluorophenyl)amino]-5-methyl-benzeneacetic acid used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 99/11605.

[000196] The compound N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,885,367.

[000197] The compound (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 6,180,651.

[000198] Cox-2 inhibitors can also be isolated and purified from natural sources. Cox-2 inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[000199] The present invention provides methods that spare or reduce the normally prescribed dosages of corticosteroids. Corticosteroids are a class of therapeutic compounds that are useful in the treatment of

inflammatory conditions. Corticosteroids inhibit the attraction of inflammatory cells to the site of an allergic reaction, upregulate β_2-receptors, block leukotriene synthesis, and inhibit cytokine production and adhesion protein activation. *See The Merck Manual, 17th edition, Sec. 6, Chapter 68, Chronic Obstructive Airway Disorders, Asthma.*

[000200] While not intended to be limiting, normally prescribed dosages for corticosteroids have been reported to range from about 0.05 mg/day to about 1 gram/day, depending upon the particular corticosteroid used. See U.S. Patent No. 6,054,487 to Sekut, *et al.* As an example, the normally prescribed dosages for one commonly prescribed inhaled corticosteroid, beclomethasone dipropionate, is from 168 µg to 336 µg per day for adults and children 6 years of age. Beclomethasone is normally prescribed as an inhaler therapy. *See* Vancenase® patient prescribing information, <http://www.sch-plough.com/documents/18780275_Vancenase_PI.pdf>. For orally ingested corticosteroids such as prednisone and prednisolone, a dosage of 0.25 - 2.0 mg/kg (usually 0.5 mg/kg) of body weight is a normally prescribed dosage in a two to four week treatment course. *See* The Merck Manual, *17th edition, Sec. 6, Chapter 68, Chronic Obstructive Airway Disorders, COPD.*

[000201] The present invention encompasses corticosteroids that are naturally occurring, synthetic, or semi-synthetic in origin. Examples of useful corticosteroids include, but are not limited to, those recited in Table 3 below.

Table 3

Table 3: Corticosteroids					
No.	**Generic Name**	**Trade Name(s)**	**Drug Class**	**Dosing**	**Reference**
A1	hydrocortisone		corticosteroid	1%	The Merck Manual, Sec. 7. Chap 83-85,17th Edition. (1999).
A2	mometasone	Nasonex® and Elocon®	corticosteroid	topical-1% nasal-50-100 mcg/spray	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A3	Fluticasone *S-(fluoromethyl)6a,9-difluoro-11b, 17-dihydroxy-16a-methyl-3-oxoandrosta-1,4-diene-17b-carbothioate, 17-propionate*	Flovent®	corticosteroid	110-1000 mcg/day	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A4	fluocinolone acetonide		corticosteroid	.01 - . 025%	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).

Table 3: Corticosteroids					
No.	**Generic Name**	**Trade Name(s)**	**Drug Class**	**Dosing**	**Reference**
A5	fluocinolone	Derma-Smoothe/FS®	corticosteroid	.01%	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A6	flurandrenolone acetonide	Cordran, Cordran SP	corticosteroid	.05%	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A7	ciclesonide	Alvesco®	corticosteroid	100 to 400 micrograms (mcg) once daily	
A8	budesonide	Rhinocort® and Rhinocort AQ®	corticosteroid	32 mcg to 200 mcg twice daily.	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A9	beclomethasone	Beconase®, Beconase AQ®, Vancenase®, Vancenase AQ DS®	corticosteroid	40 mcg to 320 mcg twice daily.	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A10	deflazacort	Calcort	corticosteroid	6.5mg to 78 mg per day.	

Table 3: Corticosteroids

No.	Generic Name	Trade Name(s)	Drug Class	Dosing	Reference
A11	flunisolide	Nasalide®, Nasarel®, Aerobid®, Aerobid®-menthol	corticosteroid	25 mcg to 250 mcg 1-2 times per day.	Physicians' Desk Reference, Medical Economics Co., 55^{th} Edition (2001).
A12	beclomethasone dipropionate	Beconase®, Beclovent®, Beconase®-AQ, Vancenase®, Vanceril®	corticosteroid	42 mcg once or twice daily.	Physicians' Desk Reference, Medical Economics Co., 55^{th} Edition (2001).
A13	betamethasone	Celestone, Soluspan®, Diprolene®, Diprosone®	corticosteroid	topical cream – 0.05% and injeciton-3mg/mL.	Physicians' Desk Reference, Medical Economics Co., 55^{th} Edition (2001).
A14	betamethasone valerate		corticosteroid		Physicians' Desk Reference, Medical Economics Co., 55^{th} Edition (2001).
A15	methylprednisolone	Depo-Medrol®, Medrol®, Solu-Medrol®	corticosteroid	oral: 4 mg – 16 mg and injectable: 40 mg/mL to 80 mg/mL	Physicians' Desk Reference, Medical Economics Co., 55^{th} Edition (2001).

Table 3: Corticosteroids

No.	Generic Name	Trade Name(s)	Drug Class	Dosing	Reference
A16	dexamethasone	Decadron®, Maxidex®	corticosteroid	oral: 0.5 – 4 mg, injectable – 4 – 10 mg/mL.	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A17	prednisolone	Pediapred®, Prelone®	corticosteroid	ophthalmic suspension: 1% and oral liquid: 3 mg/mL.	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A18	hyrdrocortisone	Cortisol, Anusol-HC®, Cetacort®, Cortef®, Cortenema®, Cortifoam®	corticosteroid	oral: 5 – 20 mg and cream/lotion: 1.0%.	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A19	triamcinolone	Nasacort®, Nasacort, AQ® TriNasal®, Azmacort®, Aristocort®, Aristospan®	corticosteroid	50 to 500 mcg given one to four times daily for inhalation. and for creams: 0.025 – 0.5%.	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A20	clobetasol	Temovate®	corticosteroid		Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).

Table 3: Corticosteroids

No.	Generic Name	Trade Name(s)	Drug Class	Dosing	Reference
A21	cortisone		corticosteroid	25 to 30 mg per day.	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A22	corticosterone		corticosteroid		Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A23	clocortolone	Cloderm Cream®	corticosteroid	0.01%	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A24	dihydroxycortisone		corticosteroid		
A25	alclometasone	Aclovate®	corticosteroid	0.05%	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A26	amcinonide	Cyclocort®	corticosteroid	0.1%	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A27	fluorometholone	FML Forte®	corticosteroid	0.25%	
A28	halcinonide	Halog ointment	corticosteroid	0.1%	
A29	fluprednidene		corticosteroid		

Table 3: Corticosteroids

No.	Generic Name	Trade Name(s)	Drug Class	Dosing	Reference
A30	halobetasol	Ultravate Cream®	corticosteroid	0.5 mg/g	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A31	desonide	Desowen®	corticosteroid		Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A32	diflorasone	Florone®, Maxiflor®, Psorcon®	corticosteroid	0.5 mg/g	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A33	flurandrenolide	Cordran®	corticosteroid	0.025 - 0.05 %	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A34	fluocinonide	Lidex® and Licon®	corticosteroid	0.5 mg/g	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A35	prednicarbate	Dermatop®	corticosteroid	0.1%	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).

Table 3: Corticosteroids

No.	Generic Name	Trade Name(s)	Drug Class	Dosing	Reference
A36	desoximetasone	Topicort®	corticosteroid	0.05 – 0.25 %	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A37	fluprednisolone		corticosteroid		
A38	prednisone	Deltasone®, Orasone®	corticosteroid	2.5 – 200 mg once daily.	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A39	azelastine	Astelin®, Optivar®	corticosteroid	0.05%	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A40	dexamethasone 21-phosphate		corticosteroid		
A41	fludrocortisone	Florinef®	corticosteroid	0.1 – 0.2 mg once daily.	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A42	flumethasone		corticosteroid		

Table 3: Corticosteroids					
No.	**Generic Name**	**Trade Name(s)**	**Drug Class**	**Dosing**	**Reference**
A43	fluocinonide plus desonide		corticosteroid		Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A44	fluocortolone		corticosteroid		
A45	halopredone		corticosteroid		
A46	hydrocortisone 17-valerate		corticosteroid		
A47	hydrocortisone 17-butyrate		corticosteroid		
A48	hydrocortisone 21-acetate		corticosteroid		
A49	prednisolone 21-phosphate		corticosteroid		
A50	clobetasol butyrate and clobetasol propionate	Cormax®, Embeline®, Temovate®	corticosteroids	0.05%	Physicians' Desk Reference, Medical Economics Co., 55th Edition (2001).
A51	diflucortolone valerate		corticosteroid		
A52	flucortolone		corticosteroid		

[000202] Included in the present invention are methods, compositions and kits that include a Cox-2 inhibitor and a corticosteroid. Any combination of Cox-2 inhibitors and corticosteroids can be used. In a preferred embodiment, one or more Cox-2 inhibitors be combined with any one or more of the corticosteroids selected from hydrocortisone, mometasone, fluticasone, fluocinolone acetonide, fluocinolone, flurandrenolone acetonide, ciclesonide, budesonide, beclomethasone, deflazacort, flunisolide, beclomethasone dipropionate, betamethasone, betamethasone valerate, methyl-prednisolone, dexamethasone, prednisolone, cortisol, triamcinolone, clobetasol, clobetasol propionate, clobetasol butyrate, cortisone, corticosterone, clocortolone, dihydroxycortisone, alclometasone, amcinonide, diflucortolone valerate, flucortolone, fluprednidene, fluandrenolone, fluorometholone, halcinonide, halobetasol, desonide, diflorasone, flurandrenolide, fluocinonide, prednicarbate, desoximetasone, fluprednisolone, prednisone, azelastine, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, halopredone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate, prednisolone, prednisolone 21-phosphate, clobetasol propionate, triamcinolone acetonide, and mixtures thereof.

[000203] Further preferred is that one or more Cox-2 selective inhibitors be combined with any one or more of the corticosteroids selected from hydrocortisone, mometasone, fluticasone, fluocinolone acetonide, fluocinolone, flurandrenolone acetonide, ciclesonide, budesonide, beclomethasone, deflazacort, flunisolide, beclomethasone dipropionate, betamethasone, betamethasone valerate, methyl-prednisolone, dexamethasone, prednisolone, cortisol, triamcinolone, clobetasol, clobetasol propionate, clobetasol butyrate, cortisone, corticosterone, clocortolone, dihydroxycortisone, alclometasone, amcinonide, diflucortolone valerate, flucortolone, fluprednidene, fluandrenolone, fluorometholone, halcinonide, halobetasol, desonide, diflorasone, flurandrenolide, fluocinonide, prednicarbate, desoximetasone,

fluprednisolone, prednisone, azelastine, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, halopredone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate, prednisolone, prednisolone 21-phosphate, clobetasol propionate, triamcinolone acetonide, and mixtures thereof.

[000204] Even more preferred is that a Cox-2 selective inhibitor selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, meloxicam, rofecoxib, lumiracoxib, etoricoxib, RS 57067, T-614, BMS-347070, JTE-522, S-2474, SVT-2016, CT-3, ABT-963, SC-58125, nimesulide, flosulide, NS-398, L-745337, RWJ-63556, L-784512, darbufelone, CS-502, LAS-34475, LAS-34555, S-33516 and SD-8381, be combined with any of one or more corticosteroids selected from the group consisting of hydrocortisone, mometasone, fluticasone, fluocinolone acetonide, fluocinolone, flurandrenolone acetonide, ciclesonide, budesonide, beclomethasone, deflazacort, flunisolide, beclomethasone dipropionate, betamethasone, betamethasone valerate, methyl-prednisolone, dexamethasone, prednisolone, cortisol, triamcinolone, clobetasol, clobetasol propionate, clobetasol butyrate, cortisone, corticosterone, clocortolone, dihydroxycortisone, alclometasone, amcinonide, diflucortolone valerate, flucortolone, fluprednidene, fluandrenolone, fluorometholone, halcinonide, halobetasol, desonide, diflorasone, flurandrenolide, fluocinonide, prednicarbate, desoximetasone, fluprednisolone, prednisone, azelastine, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, halopredone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate, prednisolone, prednisolone 21-phosphate, clobetasol propionate, triamcinolone acetonide, and mixtures thereof.

[000205] Still further preferred is that a Cox-2 selective inhibitor selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib and lumiracoxib, be combined with any of one or more corticosteroids selected from the group consisting of hydrocortisone, mometasone, fluticasone, fluocinolone acetonide,

fluocinolone, flurandrenolone acetonide, ciclesonide, budesonide, beclomethasone, deflazacort, flunisolide, beclomethasone dipropionate, betamethasone, betamethasone valerate, methyl-prednisolone, dexamethasone, prednisolone, cortisol, triamcinolone, clobetasol, clobetasol propionate, clobetasol butyrate, cortisone, corticosterone, clocortolone, dihydroxycortisone, alclometasone, amcinonide, diflucortolone valerate, flucortolone, fluprednidene, fluandrenolone, fluorometholone, halcinonide, halobetasol, desonide, diflorasone, flurandrenolide, fluocinonide, prednicarbate, desoximetasone, fluprednisolone, prednisone, azelastine, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, halopredone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate, prednisolone, prednisolone 21-phosphate, clobetasol propionate and triamcinolone acetonide.

[000206] Even further preferred is that celecoxib be combined with any of one or more corticosteroids selected from the group consisting of hydrocortisone, mometasone, fluticasone, fluocinolone acetonide, fluocinolone, flurandrenolone acetonide, ciclesonide, budesonide, beclomethasone, deflazacort, flunisolide, beclomethasone dipropionate, betamethasone, betamethasone valerate, methyl-prednisolone, dexamethasone, prednisolone, cortisol, triamcinolone, clobetasol, clobetasol propionate, clobetasol butyrate, cortisone, corticosterone, clocortolone, dihydroxycortisone, alclometasone, amcinonide, diflucortolone valerate, flucortolone, fluprednidene, fluandrenolone, fluorometholone, halcinonide, halobetasol, desonide, diflorasone, flurandrenolide, fluocinonide, prednicarbate, desoximetasone, fluprednisolone, prednisone, azelastine, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, halopredone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate, prednisolone, prednisolone 21-phosphate, clobetasol propionate, triamcinolone acetonide, and mixtures thereof.

[000207] In preferred embodiments, any combination of the Cox-2 inhibitors and corticosteroids that are described above can be used in the novel methods, compositions, pharmaceutical compositions and kits of the present invention.

[000208] In a preferred embodiment, the Cox-2 selective inhibitor, celecoxib can be combined with any of the corticosteroids cited in Table 3, including, for example, the corticosteroid, fluticasone.

[000209] In another preferred embodiment, the present invention encompasses a novel therapeutic composition comprising a Cox-2 inhibitor and a corticosteroid.

[000210] A novel therapeutic composition that has been found to be useful for the purpose of preventing or treating a corticosteroid-responsive disease or disorder in a subject that is in need of such prevention or treatment, includes a Cox-2 inhibitor and a corticosteroid.

[000211] Each of the Cox-2 inhibitors and corticosteroids of the present invention can be supplied in the form of a salt, or prodrug, if desirable. Cox-2 inhibitors and corticosteroids that are useful in the present invention can be of any purity or grade, as long as the preparation is of a quality suitable for pharmaceutical use. The Cox-2 inhibitors and corticosteroids can be provided in pure form, or it can be accompanied with impurities or commonly associated compounds that do not affect its physiological activity or safety. The Cox-2 inhibitors and corticosteroids can be supplied as a pure compound, or in the form of a pharmaceutically acceptable salt. The Cox-2 inhibitors and corticosteroids can be supplied in the form of a prodrug, an isomer, a mixed isomer, a racemic mixture, or in any other chemical form or combination that, under physiological conditions, provides the corticosteroid.

[000212] In the methods of the present invention, a Cox-2 inhibitor and a corticosteroid are administered to a subject according to standard routes of drug delivery that are well known to one of ordinary skill in the art. The particular route and dosage of the Cox-2 inhibitor and the corticosteroid depend upon the needs of the subject being treated, the type of treatment,

the efficacy of the compound and the degree of disease severity in the subject. *See* U.S. Patent No. 6,054,487 to Sekut, *et al.*

[000213] The compositions of the present invention can comprise a Cox-2 inhibitor and a corticosteroid as an active ingredient or a pharmaceutically acceptable salt, thereof, and also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. When the Cox-2 inhibitor and corticosteroid are supplied along with a pharmaceutically acceptable carrier, a pharmaceutical composition is formed. A pharmaceutical composition of the present invention is directed to a composition suitable for the reduction or amelioration or prevention of steroid-related side-effects and/or for preventing or treating a corticosteroid-responsive disease or disorder in a subject. Also useful in the present invention are pharmaceutical compositions, which include a pharmaceutically acceptable carrier in addition to the Cox-2 inhibitor and the corticosteroid.

[000214] In a preferred embodiment, the present invention encompasses a pharmaceutical composition for preventing or treating a a corticosteroid-responsive disease or disorder in a subject comprising a Cox-2 inhibitor, a corticosteroid, and a pharmaceutically acceptable carrier.

[000215] The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product.

[000216] Pharmaceutically acceptable carriers and excipients include, but are not limited to, physiological saline, Ringer's solution, phosphate solution or buffer, buffered saline and other carriers known in the art.

[000217] Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective.

[000218] In one embodiment the Cox-2 inhibitor and the corticosteroid are administered to a subject together in one pharmaceutical carrier. In another embodiment, the Cox-2 inhibitor and the corticosteroid are administered separately.

[000219] The pharmaceutically acceptable carrier can also be selected on the basis of the desired route of administration of the compound. For example, in a preferred embodiment the carrier is suitable for oral administration.

[000220] The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, hydrochloric, trifluoroacetic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

[000221] Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts.

[000222] Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine,

methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[000223] Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences.

[000224] Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N, N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[000225] All of the above salts and ions can be prepared by those skilled in the art by conventional means from the corresponding compounds of the present invention.

[000226] In the present invention, a Cox-2 inhibitor and a corticosteroid are administered to a subject according to standard routes of drug delivery that are well known to one of ordinary skill in the art. The particular route and dosage of the Cox-2 inhibitor and the corticosteroid depend upon the needs of the subject being treated, the type of treatment or prevention, the efficacy of the compound and the degree of disease severity in the subject.

[000227] The pharmaceutical compositions may be administered enterally and parenterally. Oral (intra-gastric) is a preferred route of

administration. Pharmaceutically acceptable carriers can be in solid dosage forms for the methods of the present invention, which include tablets, capsules, pills, and granules, which can be prepared with coatings and shells, such as enteric coatings and others well known in the art. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs.

[000228] Enteral administration includes solution, tablets, sustained release capsules, enteric-coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

[000229] Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

[000230] Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, maize starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[000231] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as

such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[000232] Aqueous suspensions can be produced that contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[000233] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[000234] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[000235] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[000236] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending

agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[000237] Syrups and elixirs containing the Cox-2 inhibitor and corticosteroid may be formulated with sweetening agents, for example glycerol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[000238] The subject method of prescribing a Cox-2 inhibitor and a corticosteroid and compositions comprising the same can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art.

[000239] Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents, which have been mentioned above or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

[000240] In preferred embodiments, administration of the Cox-2 inhibitor and corticosteroid can also be by inhalation, in the form of aerosols or solutions for nebulizers. Therefore, in one embodiment, the Cox-2 inhibitor and the corticosteroid are administered by direct inhalation

into the respiratory system of a subject for delivery as a mist or other aerosol or dry powder. Delivery of drugs or other active ingredients directly to the subject's lungs provides numerous advantages including, providing an extensive surface area for drug absorption, direct delivery of therapeutic agents to the disease site in the case of regional drug therapy, eliminating the possibility of drug degradation in the subject's intestinal tract (a risk associated with oral administration), and eliminating the need for repeated subcutaneous injections.

[000241] Aerosols of liquid particles comprising the active materials may be produced by any suitable means, such as inhalatory delivery systems. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier. The carrier is typically water, and most preferably sterile, pyrogen-free water, or a dilute aqueous alcoholic solution, preferably made isotonic, but may be hypertonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not made sterile, for example, methyl hydroxybenzoate, as well as antioxidants, flavoring agents, volatile oils, buffering agents and surfactants, which are normally used in the preparation of pharmaceutical compositions.

[000242] Aerosols of solid particles comprising the active materials may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration.

[000243] One type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include

finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened *in situ* and the powder delivered by means of air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active materials, a suitable powder diluent, such as lactose, and an optional surfactant.

[000244] A second type of aerosol generator is a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the Cox-2 inhibitor and the corticosteroid in a liquified propellant. During use, the metered dose inhaler discharges the formulation through a valve, adapted to deliver a metered volume, to produce a fine particle spray containing the active materials. Any propellant may be used for aerosol delivery, including both chlorofluorocarbon-containing propellants and non-chlorofluorocarbon-containing propellants.

[000245] A third type of aerosol generator is a electrohydrodynamic (EHD) aerosol generating device, which has the advantage of being adjustable to create substantially monomodal aerosols having particles more uniform in size than aerosols generated by other devices or methods. Typical EHD devices include a spray nozzle in fluid communication with a source of liquid to be aerosolized, at least one discharge electrode, a first voltage source for maintaining the spray nozzle at a negative (or positive) potential relative to the potential of the discharge electrode, and a second voltage source for maintaining the discharge electrode at a positive (or negative) potential relative to the potential of the spray nozzle.

[000246] Most EHD devices create aerosols by causing a liquid to form droplets that enter a region of high electric field strength. The electric field then imparts a net electric charge to these droplets, and this net

electric charge tends to remain on the surface of the droplet. The repelling force of the charge on the surface of the droplet balances against the surface tension of the liquid in the droplet, thereby causing the droplet to form a cone-like structure known as a Taylor Cone. In the tip of this cone-like structure, the electric force exerted on the surface of the droplet overcomes the surface tension of the liquid, thereby generating a stream of liquid that disperses into a many smaller droplets of roughly the same size. These smaller droplets form a mist which constitutes the aerosol cloud that the user ultimately inhales.

[000247] In a preferred embodiment, the administration of the compositions of the present invention can also be by a rectal route of delivery. Rectal routes of delivery are in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature, but liquid at the rectal temperature and will therefore, melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[000248] Also encompassed by the present invention is buccal or "sub-lingual" administration, which includes lozenges or a chewable gum comprising the compounds, set forth herein. The compounds can be deposited in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compounds in an inert base such as gelatin and glycerin or sucrose and acacia.

[000249] The present invention further encompasses intranasal administration comprising the compounds set forth herein. Intranasal dosage forms include, but are not limited to, aerosols, drops, gels, powders, and mixtures thereof.

[000250] Other methods for administration of the Cox-2 inhibitor and the corticosteroid include dermal patches that release the medicaments directly into a subject's skin.

[000251] Topical delivery systems are also encompassed by the present invention and include ointments, powders, sprays, creams, jellies, collyriums, solutions or suspensions.

[000252] The compositions of the present invention can optionally be supplemented with additional agents such as, for example, viscosity enhancers, preservatives, surfactants and penetration enhancers.

[000253] Viscosity is an important attribute of many medications. Drops that have a high viscosity tend to stay in the body for longer periods and thus, increase absorption of the active compounds by the target tissues or increase the retention time. Such viscosity-building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methylcellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents know to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

[000254] Preservatives are optionally employed to prevent microbial contamination during use. Suitable preservatives include polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-1 as the antimicrobial preservative is preferred. Typically, such preservatives are employed at a level of from 0.001% to 1.0% by weight.

[000255] The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (*e.g.* Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically, such co-solvents are employed at a level of from 0.01% to 2% by weight.

[000256] A penetration enhancer is an agent used to increase the permeability of the skin to an active agent to increase the rate at which the drug diffuses through the skin and enters the tissues and bloodstream. Thus, in one embodiment of the present invention, a penetration enhancer may be added to the Cox-2 inhibitor and/or the corticosteroid topical composition.

[000257] Examples of penetration enhancers suitable for use with the compositions of the present invention include: alcohols, such as ethanol and isopropanol; polyols, such as n-alkanols, limonene, terpenes, dioxolane, propylene glycol, ethylene glycol, other glycols, and glycerol; sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, dimethylacetamide; esters, such as isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl proprionate, and capric/caprylic triglycerides; ketones; amides, such as acetamides; oleates, such as triolein; various surfactants, such as sodium lauryl sulfate; various alkanoic acids, such as caprylic acid; lactam compounds, such as azone; alkanols, such as oleyl alcohol; dialkylamino acetates, and admixtures thereof.

[000258] In preferred embodiments, the corticosteroid medications are administered to a subject via a route that is selected from the group consisting of nasal sprays, metered-dose-inhalers, oral forms (pills or syrups), injections, topical forms, and intravenous (IV) solutions, while the Cox-2 inhibitor is administered to the subject via an oral form (pills or syrups).

[000259] Pharmaceutically acceptable excipients and carriers encompass all the foregoing and the like. The above considerations concerning effective formulations and administration procedures are well known in the art and are described in standard textbooks. *See e.g.* Gennaro, A. R., Remington: The Science and Practice of Pharmacy, 20th Edition, (Lippincott, Williams and Wilkins), 2000; Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman, *et al.*, Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, *et al.*, Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

[000260] It is preferred that the amount of the Cox-2 inhibitor and the amount of the corticosteroid that are administered to a subject together comprise an effective amount of the combination of the two compounds.

Preferably, the amount of the combination is a therapeutically effective amount.

[000261] As used herein, an "effective amount" means the dose or effective amount to be administered to a subject and the frequency of administration to the subject which is readily determined by one having ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances. The dose or effective amount to be administered to a subject and the frequency of administration to the subject can be readily determined by one of ordinary skill in the art by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to, the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the subject to be treated, and other relevant circumstances.

[000262] As used herein, the term "therapeutically effective" is intended to qualify the amount of each agent for use in therapy which will achieve the goal of preventing, or improvement in the severity of, the disorder being treated, while avoiding adverse side effects typically associated with monotherapies with corticosteroids.

[000263] An inflammatory symptom is considered ameliorated or improved if any benefit is achieved, no matter how slight. An amount of either a Cox-2 or corticosteroid that causes a decrease in the frequency of incidence is "prophylactically effective", where the term "prophylactic" refers to the prevention of disease, whereas the term "therapeutic" refers to the effective treatment of existing disease. Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[000264] Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage has been described above, although the limits that were identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

[000265] Therefore, for purposes of the present invention, it is preferred to dose the Cox-2 inhibitor in an amount sufficient to provide a steroid-sparing benefit when given as a combination therapy to a subject in need of such treatment, wherein the amount of the Cox-2 inhibitor which is administered and the amount of the corticosteroid which is administered together comprise a therapeutically effective amount of the combination.

[000266] The appropriate dosage level of a Cox-2 inhibitor will generally be from about 0.01 mg/kg to about 140 mg/kg subject body weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 mg/kg to about 25 mg/kg per day; more preferably about 0.5 mg to about 10 mg/kg per day.

[000267] In larger mammals, for example humans, a typical indicated dose is about 0.5 mg to 7 grams orally per day. A compound may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day.

[000268] The amount of the Cox-2 inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 7 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms for the Cox-2 inhibitor will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

[000269] In a preferred embodiment, the methods of the present invention encompass any detectable reduction in the dosage of corticosteroids normally required to treat a subject in need of such treatment provided the lowered dosage of corticosteroids does not substantially worsen the subject's inflammatory symptoms (steroid-sparing benefit).

[000270] One of ordinary skill in the art will know how to measure and quantify the symptoms of inflammation. For example, the degree and severity of asthma and COPD can be determined by measuring lung expiratory flow volume and expiratory flow rates. Measurement can be accomplished with, for example, a spirometer, flow volume loop, or pneumotach, before and after each of the treatments. Use of spirometry is a standard test for determining the efficacy of Cox-2 inhibitors and corticosteroids after administration to a subject suffering from a pulmonary inflammatory disorder. A device called a spirometer is used to measure how much air the lungs can hold and how well the respiratory system is able to move air into and out of the lungs.

[000271] Spirometry is a medical test that measures the physical volume of air an individual forcibly inhales or exhales into a device. The objective of spirometry is to assess ventilatory function. An estimate of flow rate, or the rate at which the volume is changing as a function of time can also be calculated with spirometery. *See* College of Physicians and Surgeons of Alberta, "*Guidelines For Spirometry & Flow Volume Measurements*"(1998). <www.cpsa.ab.ca/qoc/Guidelines%20for%20Spirometry%20&%20Flow%20Volume%20Measurements.doc>. Thus, with the methods of the present invention, spirometric comparisons of pulmonary airflow before and after treatment will elucidate similarities and differences that enable one of skill to determine the effectiveness of the treatment methods.

[000272] Common parameters that spirometry measures are Forced Vital Capacity (FVC) - the maximum volume of air, measured in liters that can be forcibly and rapidly exhaled. Another parameter is Forced

Expiratory Volume (FEV1) - the volume of air expelled in the first second of a forced expiration. Normal parameters for a subject not suffering from an inflammatory disorder such as asthma or COPD is: Tidal volume - 5 to 7 milliliters per kilogram of body weight; Expiratory reserve volume - 25% of vital capacity; Inspiratory capacity - 75% of vital capacity forced expiratory volume - 75% of vital capacity after 1 second, 94% after 2 seconds, and 97% after 3 seconds. *Healthatoz.com*, wellness, test & procedures, spirometry <http://www.healthatoz.com /atoz/TestProcedures/TPspirometry.html>.

[000273] Spirometry results are expressed as a percentage, and are considered abnormal if less than 80% of the normal predicted value. An abnormal result usually indicates the presence of some degree of obstructive lung disease such as COPD and chronic bronchitis, or restrictive lung disease such as pulmonary fibrosis or asthma.

[000274] The Cox-2 inhibitor and corticosteroid are administered to a subject in a manner that reduces the dosage of the corticosteroid over time and, thus, ameliorates any steroid rebound effect associated with administration of reduced dosages of the corticosteroid. Thus, a steroid-sparing benefit will result from the synergistic addition of another medication that can help keep a disorder under control while corticosteroids are being tapered.

[000275] For example, the dosage of the Cox-2 inhibitor could be held steady or increased slightly while the dosage of the corticosteroid is gradually reduced. In particular, a subject that has developed resistance over time to corticosteroid therapy alone will benefit from the gradual reduction in corticosteroid dosage, while simultaneously being treated with a Cox-2 inhibitor dosage. In yet another embodiment, the Cox-2 inhibitor and corticosteroid are administered to a subject where the inflammatory disorder being treated is substantially resistant to corticosteroid therapy alone.

[000276] As used herein, the term "subject" for purposes of treatment includes any subject, and preferably is a subject who is in need of a

reduction in the required dosage of a corticosteroid that is normally administered to the subject for the prevention or treatment of pain, inflammation or an inflammation-related disorder. For purposes of prevention, the subject is any subject, and preferably is a subject that is at risk for, or is predisposed to, developing side-effects and/or a steroid-rebound effect (*e.g.* a sudden termination of corticosteroid therapy) from the administration of a corticosteroid for the prevention or treatment of pain, inflammation, or an inflammation-related disorder.

[000277] As used herein, the terms "subject who is in need of a reduction in the required dosage of a corticosteroid that is normally administered to the subject for the prevention or treatment of pain, inflammation or an inflammation-related disorder" refer to any subject who is being administered a corticosteroid medication. The terms "subject who is in need of a reduction in the required dosage of a corticosteroid that is normally administered to the subject for the prevention or treatment of pain, inflammation or an inflammation-related disorder" also refer to any subject that requires a lower dose of corticosteroids. In addition, the terms "subject who is in need of a reduction in the required dosage of a corticosteroid that is normally administered to the subject for the prevention or treatment of pain, inflammation or an inflammation-related disorder," means any subject who requires a reduction in the side-effects of a corticosteroid medication. In addition, the terms "subject who is in need of a reduction in the required dosage of a corticosteroid that is normally administered to the subject for the prevention or treatment of pain, inflammation or an inflammation-related disorder," means any subject who requires the prevention of and/or improvement of a steroid-rebound effect. Furthermore, the terms "subject who is in need of a reduction in the required dosage of a corticosteroid that is normally administered to the subject for the prevention or treatment of pain, inflammation or an inflammation-related disorder," means any subject who requires improved tolerability to corticosteroids for pain or inflammation therapy. As used herein, the terms "subject in need of a corticosteroid"

refer to any subject who is in need of the prevention or treatment of pain, inflammation or an inflammation-related disorder. As used herein, the terms "subject that is presently receiving a corticosteroid" refer to any subject who is being administered a corticosteroid medication.

[000278] As used herein, the terms "predisposed to side-effects and/or a steroid-rebound effect from administration of a corticosteroid medication" and "at risk for side-effects and/or a steroid-rebound effect from administration of a corticosteroid medication," both of which are used interchangeably herein, mean any subject at risk for developing side-effects and/or a steroid-rebound effect from administration of a corticosteroid medication. The subject may be a human subject who is at risk for developing side-effects and/or a steroid-rebound effect from administration of a corticosteroid medication. The subject may be at risk due to genetic predisposition, diet, age, sex, exposure to a potentially traumatic environment, immunosuppression, immunodeficiency, exposure to pain or inflammation-causing agents, and the like.

[000279] The method of the present invention is useful for, but not limited to, lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and/or treatment of pain or inflammation regardless of the underlying cause of the pain or inflammation. The method of the present invention is also useful for, but not limited to, lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and/or treatment of inflammation-related disorders and such inflammation-related disorders as arthritis. For example, the compounds described herein would be useful for lowering the required dosages of corticosteroids that are normally administered to a subject for the treatment of any inflammation-related disorder described below, such as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. The compounds described herein would also be useful for lowering the required dosages of corticosteroids that are normally administered to a

subject for the treatment of an inflammation-related disorder in a subject suffering from such an inflammation-associated disorder.

[000280] In preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and/or treatment of inflammation-related disorders. As used herein, the terms "inflammation-related disorder" or "inflammation disorder" are meant to include, without limitation, each of the symptoms or disorders that are mentioned below.

[000281] In preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and/or treatment of any one or more of the disorders selected from the group consisting of connective tissue and joint disorders, pain and pain-related disorders, neoplasia disorders, cardiovascular disorders, otic disorders, ophthalmic disorders, respiratory disorders, gastrointestinal disorders, angiogenesis-related disorders, immunological disorders, allergic disorders, nutritional disorders, infectious diseases and disorders, endocrine disorders, metabolic disorders, neurological and neurodegenerative disorders, psychiatric disorders, hepatic and biliary disorders, musculoskeletal disorders, genitourinary disorders, gynecologic and obstetric disorders, injury and trauma disorders, surgical disorders, dental and oral disorders, sexual dysfunction disorders, dermatologic disorders, hematological disorders, and poisoning disorders.

[000282] As used herein, the terms "neoplasia" and "neoplasia disorder", used interchangeably herein, refer to new cell growth that results from a loss of responsiveness to normal growth controls, *e.g.* to "neoplastic" cell growth. Neoplasia is also used interchangeably herein with the term "cancer" and for purposes of the present invention; cancer is one subtype of neoplasia. As used herein, the term "neoplasia disorder" also encompasses other cellular abnormalities, such as hyperplasia, metaplasia and dysplasia. The terms neoplasia, metaplasia, dysplasia

and hyperplasia can be used interchangeably herein and refer generally to cells experiencing abnormal cell growth.

[000283] Both of the terms, "neoplasia" and "neoplasia disorder", refer to a "neoplasm" or tumor, which may be benign, premalignant, metastatic, or malignant. Also encompassed by the present invention are benign, premalignant, metastatic, or malignant neoplasias. Also encompassed by the present invention are benign, premalignant, metastatic, or malignant tumors. Thus, all of benign, premalignant, metastatic, or malignant neoplasia or tumors are encompassed by the present invention and may be referred to interchangeably, as neoplasia, neoplasms or neoplasia-related disorders. Tumors are generally known in the art to be a mass of neoplasia or "neoplastic" cells. Although, it is to be understood that even one neoplastic cell is considered, for purposes of the present invention to be a neoplasm or alternatively, neoplasia.

[000284] Compounds of the invention would be useful for lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention or treatment of benign and malignant tumors/neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophogeal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Preferably, neoplasia is selected from gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers. The compounds can also be used to lower the required dosages of corticosteroids that are normally administered to a subject to treat fibrosis, which occurs with radiation

therapy. The method can be used to lower the required dosages of corticosteroids that are normally administered to a subject to treat subjects having adenomatous polyps, including those with sporadic adenomatous polyposis (SAP) or familial adenomatous polyposis (FAP). Additionally, the method can be used to lowering the required dosages of corticosteroids that are normally administered to a subject for preventing polyps from forming in subjects at risk of FAP.

[000285] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the neoplasia disorders selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, familial adenomatous polyposis, familial polyps, colon polyps, polyps, adenosarcoma, adenosquamous carcinoma, adrenocortical carcinoma, AIDS-related lymphoma, anal cancer, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bile duct cancer, bladder cancer, brain stem glioma, brain tumors, breast cancer, bronchial gland carcinomas, capillary carcinoma, carcinoids, carcinoma, carcinosarcoma, cavernous, central nervous system lymphoma, cerebral astrocytoma, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, skin cancer, brain cancer, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, esophageal cancer, Ewing's sarcoma, extragonadal germ cell tumor, fibrolamellar, focal nodular hyperplasia, gallbladder cancer, gastrinoma, germ cell tumors, gestational trophoblastic tumor, glioblastoma, glioma, glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, Hodgkin's lymphoma, hypopharyngeal cancer, hypothalamic and visual pathway glioma,

insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, intraocular melanoma, invasive squamous cell carcinoma, large cell carcinoma, islet cell carcinoma, Kaposi's sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, lentigo maligna melanomas, leukemia-related disorders, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, malignant mesothelial tumors, malignant thymoma, medulloblastoma, medulloepithelioma, melanoma, meningeal, merkel cell carcinoma, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, non-Hodgkin's lymphoma, oat cell carcinoma, oligodendroglial, oral cancer, oropharyngeal cancer, osteosarcoma, pancreatic polypeptide, ovarian cancer, ovarian germ cell tumor, pancreatic cancer, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, parathyroid cancer, penile cancer, pheochromocytoma, pineal and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm, pleuropulmonary blastoma, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, small intestine cancer, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, supratentorial primitive neuroectodermal tumors, thyroid cancer, undifferentiatied carcinoma, urethral cancer, uterine sarcoma, uveal melanoma, verrucous carcinoma, vaginal cancer, vipoma, vulvar cancer, Waldenstrom's macroglobulinemia, well differentiated carcinoma, and Wilm's tumor.

[000286] In still other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the connective tissue and joint disorders

selected from the group consisting of arthritis, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, lumbar spondylarthrosis, carpal tunnel syndrome, canine hip dysplasia, systemic lupus erythematosus, juvenile arthritis, osteoarthritis, tendonitis and bursitis.

[000287] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the cardiovascular disorders selected from the group consisting of myocardial ischemia, hypertension, hypotension, heart arrhythmias, pulmonary hypertension, hypokalemia, vascular diseases, vascular rejection, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, including venous thrombosis, angina including unstable angina, coronary plaque inflammation, cardiac ischemia, myocardial infarction, cardiac remodeling, cardiac fibrosis, myocardial necrosis, aneurysm, arterial fibrosis, embolism, vascular plaque inflammation, vascular plaque rupture, bacterial-induced inflammation and viral induced inflammation, edema, swelling, fluid accumulation, cirrhosis of the liver, Bartter's syndrome, myocarditis, arteriosclerosis, atherosclerosis, calcification (such as vascular calcification and valvar calcification), coronary artery disease, heart failure, congestive heart failure, shock, arrhythmia, left ventricular hypertrophy, angina, diabetic nephropathy, kidney failure, eye damage, migraine headaches, aplastic anemia, cardiac damage, diabetic cardiac myopathy, renal insufficiency, renal injury, renal arteriopathy, peripheral vascular disease, cognitive dysfunction, stroke, headache, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

[000288] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for

the prevention and treatment of the metabolic disorders selected from the group consisting of obesity, overweight, type I and type II diabetes, hypothyroidism, and hyperthyroidism.

[000289] In other preferred embodiments, the methods and compositions of the present invention lower the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the respiratory disorders selected from the group consisting of asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary edema, pulmonary embolism, pneumonia, pulmonary sarcoisosis, silicosis, pulmonary fibrosis, respiratory failure, acute respiratory distress syndrome and emphysema.

[000290] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the angiogenesis-related disorders selected from the group consisting of angiofibroma, neovascular glaucoma, arteriovenous malformations, arthritis, osler-weber syndrome, atherosclerotic plaques, psoriasis, corneal graft neovascularization, pyogenic granuloma, delayed wound healing, retrolental fibroplasias, diabetic retinopathy, scleroderma, granulations, solid tumors, hemangioma, trachoma, hemophilic joints, vascular adhesions, hypertrophic scars, age-related macular degeneration, coronary artery disease, stroke, cancer, AIDS complications, ulcers and infertility.

[000291] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the infectious diseases and disorders selected from the group consisting of viral infections, bacterial infections, prion infections, spirochetes infections, mycobacterial infections, rickettsial infections, chlamydial infections, parasitic infections and fungal infections.

[000292] In still further embodiments, the methods and compositions of the present invention encompass lowering the required dosages of

corticosteroids that are normally administered to a subject for the prevention and treatment of the infectious diseases and disorders selected from the group consisting of hepatitis, HIV (AIDS), small pox, chicken pox, common cold, bacterial influenza, viral influenza, warts, oral herpes, genital herpes, herpes simplex infections, herpes zoster, bovine spongiform encephalopathy, septicemia, streptococcus infections, staphylococcus infections, anthrax, severe acquired respiratory syndrome (SARS), malaria, African sleeping sickness, yellow fever, chlamydia, botulism, canine heartworm, rocky mountain spotted fever, lyme disease, cholera, syphilis, gonorrhea, encephalitis, pneumonia, conjunctivitis, yeast infections, rabies, dengue fever, Ebola, measles, mumps, rubella, West Nile virus, meningitis, gastroenteritis, tuberculosis, hepatitis, and scarlet fever.

[000293] The present invention also provides a therapy comprising a Cox-2 inhibitor in combination with a corticosteroid, which encompasses lowering the required dosages of corticosteroids that are normally administered to a subject for the treatment and prevention of such neurodegenerative disorder symptoms as, for example, dementia, aphasia, memory loss, depression, apraxia, anxiety, personality disorders, agnosia, and hallucinations in a subject suffering from such symptoms.

[000294] As used herein, the terms "neurodegenerative disorder" is defined as having any abnormality of one or more nerves, a post-surgical condition of any tissue that is comprised of nerves, or an age-related condition of one or more nerves. As used herein, the term "neuro" or "nerve" includes any component or structure found within or on the central nervous system or peripheral nervous system, including, but not limited to, neurons, brain tissue, spinal cord tissue, glial cells, astrocytes, dendrites, cholinergic receptors, adrenergic receptors, gaba receptors, serotoninergic (5-HT) receptors, glutamate receptors, endorphin-enkephalin (opioid) receptors, Schwann cells, axons, oligodendrocytes, microglia, ependyma, myelin sheaths, and any other neurological tissue within a subject's body.

[000295] The terms "neurodegenerative disorder" also include any complications that arise from having such a disorder. For example, many chronic neurodegenerative disorders are often associated with complications, such as, for example, complications caused by immobility, muscle contractures, reduced life span, opportunistic infections, and pressure sores, any of which may eventually arise from having a chronic or recurring neurodegenerative disorder. Behavioral neurodegenerative disorder complications include hostility, aggression, agitation, wandering, and uncooperativeness. Psychiatric complications include depression, anxiety, paranoid reactions, delusions, and hallucinations. Thus, the terms "neurodegenerative disorder complication" and "neurodegenerative disorder-related complication," used interchangeably herein, includes any subsequent disease, disorder, injury or condition that may arise from having a neurodegenerative disorder. The term "neurodegenerative disorder-related complication" refers to any condition where developing a neurodegenerative disorder is a risk factor for developing health complications.

[000296] Neurodegenerative disorders may arise in a subject via several determinants including chronic substance abuse, vascular disease, and inadequate consumption of vitamins, infectious agents, causative agents, brain cancer, mental or physical trauma, brain trauma and genetics. The methods and compositions of the present invention are intended to treat a subject suffering from a neurodegenerative disorder regardless of how the disorder first arose.

[000297] In preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the neurodegenerative disorders selected from the group consisting of cortical dementias, general dementia, old-age, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementias, stroke, coma, seizures, epilepsy, amnesia, hypovolemic shock, phenylketonuria,

aminoacidurias, Tay-Sachs, Niemann-Pick, Gaucher's diseases, Hurler's syndrome, Krabbe's disease, leukodystrophies, traumatic shock, reperfusion injury, multiple sclerosis, AIDS, associated dementia, neuron toxicity, head trauma, adult respiratory disease (ARDS), acute spiral cord injury, Parkinson's Disease, frontotemporal dementia, Pick's disease, ischemia, palsy, supranuclear palsy, corticobasal degeneration, multi-infarct dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, delirium, headaches, migraine headaches, Parkinson's disease, memory loss, senility, amyotrophy, ALS, muscular dystrophies, epilepsy, schizophrenia, depression, anxiety, anxiety, autism, phobias, spongiform encephalopathies, Huntington's Chorea, ischemia, obsessive-compulsive disorder, anxiety-related disorders, stress-related disorders, psychosis, neuroendocrine system disorders, thermoregulation disorders, vasoreactive headaches, sexual dysfunction, tooth-germ morphogenesis disorders, Tourette's syndrome, autism, attention deficit disorders, hyperactivity disorders, sleep disorders, social phobias, urinary incontinence, vasospasm, stroke, eating disorders such as obesity, anorexia and bullemia, manic depression, bipolar disorders, drug addiction, alcoholism and smoking addiction. In addition, the neurodegenerative disorders that may be treated with the compositions and methods described herein, include a subject who is otherwise normal, but wishes to improve upon certain cognitive abilities, such as memory retention and thought processes.

[000298] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the dermatological disorders selected from the group consisting of acne, psoriasis, eczema, burns, poison ivy, poison oak and dermatitis.

[000299] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for

the prevention and treatment of the surgical disorders selected from the group consisting of pain and swelling following surgery, infection following surgery and inflammation following surgery.

[000300] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the gastrointestinal disorders selected from the group consisting of inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, gastritis, irritable bowel syndrome, diarrhea, constipation, dysentery, ulcerative colitis, gastric esophageal reflux, gastric ulcers, gastric varices, ulcers, and heartburn.

[000301] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the otic disorders selected from the group consisting of otic pain, inflammation, otorrhea, otalgia, fever, otic bleeding, Lermoyez's syndrome, Meniere's disease, vestibular neuronitis, benign paroxysmal positional vertigo, herpes zoster oticus, Ramsay Hunt's syndrome, viral neuronitis, ganglionitis, geniculate herpes, labyrinthitis, purulent labyrinthitis, viral endolymphatic labyrinthitis, perilymph fistulas, noise-induced hearing loss, presbycusis, drug-induced ototoxicity, acoustic neuromas, aerotitis media, infectious myringitis, bullous myringitis, otitis media, otitis media with effusion, acute otitis media, secretory otitis media, serous otitis media, acute mastoiditis, chronic otitis media, otitis extema, otosclerosis, squamous cell carcinoma, basal cell carcinoma, nonchromaffin paragangliomas, chemodectomas, globus jugulare tumors, globus tympanicum tumors, external otitis, perichondritis, aural eczematoid dermatitis, malignant external otitis, subperichondrial hematoma, ceruminomas, impacted cerumen, sebaceous cysts, osteomas, keloids, otalgia, tinnitus, vertigo, tympanic membrane infection, typanitis, otic furuncles, otorrhea, acute mastoiditis, petrositis, conductive and sensorineural hearing loss, epidural abscess, lateral sinus thrombosis,

subdural empyema, otitic hydrocephalus, Dandy's syndrome, bullous myringitis, cerumen-impacted, diffuse external otitis, foreign bodies, keratosis obturans, otic neoplasm, otomycosis, trauma, acute barotitis media, acute eustachian tube obstruction, post-otic surgery, postsurgical otalgia, cholesteatoma, conductive and sensorineural hearing loss, epidural abscess, lateral sinus thrombosis, subdural empyema and otitic hydrocephalus.

[000302] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of the ophthalmic disorders selected from the group consisting of retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue, conjunctivitis, macular degeneration, age-related macular degeneration, diabetic retinopathy, detached retina, glaucoma, vitelliform macular dystrophy type 2, gyrate atrophy of the choroid and retina, conjunctivitis, corneal infection, Fuchs' dystrophy, iridocorneal endothelial syndrome, retinitis, keratoconus, lattice dystrophy, map-dot-fingerprint dystrophy, ocular herpes, pterygium, myopia, hyperopia, and cataracts,

[000303] The combinations and methods would also be useful for lowering the required dosages of corticosteroids that are normally administered to a subject for the treatment or prevention of pain, but not limited to postoperative pain, dental pain, muscular pain, neuropathic pain and pain resulting from cancer.

[000304] In other preferred embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and treatment of menstrual cramps, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, sinus headaches, tension headaches, periarteritis nodosa, thyroiditis, myasthenia gravis, sarcoidosis, nephrotic syndrome, Bahcet's syndrome, polymyositis,

gingivitis, hypersensitivity, swelling occurring after injury, closed head injury, liver disease, and endometriosis.

[000305] In one embodiment, the combinations of the invention would be useful for lowering the required dosages of corticosteroids that are normally administered to a subject to treat arthritis, including, but not limited to, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

[000306] In other embodiments, the methods and compositions of the present invention encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention and/or treatment of any one or more of the disorders selected from the group consisting of neoplasia disorders, cardiovascular disorders, otic disorders, ophthalmic disorders, respiratory disorders, gastrointestinal disorders, angiogenesis-related disorders, immunological disorders, allergic disorders, nutritional disorders, infectious diseases and disorders, endocrine disorders, metabolic disorders, neurological and neurodegenerative disorders, psychiatric disorders, hepatic and biliary disorders, genitourinary disorders, gynecologic and obstetric disorders, injury and trauma disorders, surgical disorders, dental and oral disorders, sexual dysfunction disorders, dermatologic disorders, hematological disorders, and poisoning disorders.

[000307] In still other embodiments, the combinations of the invention would be useful for lowering the required dosages of corticosteroids that are normally administered to a subject for the treatment prevention of asthma, bronchitis, menstrual cramps, tendinitis, bursitis and skin related conditions such as psoriasis, eczema, burns and dermatitis. Combinations of the invention also would be useful for lowering the required dosages of corticosteroids that are normally administered to a subject to treat or prevent gastrointestinal conditions such as inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as colorectal cancer. Combinations of the invention would

be useful in treating inflammation in diseases and conditions such as herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

[000308] Compositions having the novel combination would also be useful for lowering the required dosages of corticosteroids that are normally administered to a subject for in the treatment or prevention of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compositions would also be useful for lowering the required dosages of corticosteroids that are normally administered to a subject for the treatment or prevention of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compositions would also be useful for lowering the required dosages of corticosteroids that are normally administered to a subject for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease.

[000309] As used herein, the terms "inflammation-associated disorder", and "Cox-2 mediated disorder" are meant to include, without limitation, each of the symptoms or disorders that is mentioned above.

[000310] The methods and compositions of the present invention not only encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the prevention or treatment of pain, inflammation or inflammation-related disorders in humans, but also in several animals. For example, many animals also suffer adverse consequences related to pain and inflammation and inflammation-related

disorders. Moreover, many inflammation-related disorders in dogs respond to the same treatment used in humans.

[000311] Accordingly, besides being useful for humans, the methods and compositions of the present invention also encompass lowering the required dosages of corticosteroids that are normally administered to a subject for the treatment and prevention of pain or inflammation, and in preferred embodiments, inflammation-related disorders, in other mammals, including horses, dogs, cats, rats, mice, sheep, pigs, cattle, hamsters, gerbils, and the like. Thus, it is preferred that the subject is an animal, and yet more preferred, the subject is a mammal. Preferably, the mammal is a human.

[000312] The present invention further comprises kits that are suitable for use in performing the methods of treatment or prevention described above. In one embodiment, the kit contains a first dosage form comprising one or more of the Cox-2 inhibitors or prodrugs thereof identified above and a second dosage form comprising a corticosteroid in one or more of the forms identified above, in quantities sufficient to carry out the methods of the present invention. Preferably, the first dosage form and the second dosage form together comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of side-effects or a steroid-rebound effect for the administration of corticosteroid medications.

[000313] The following examples describe embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

EXAMPLE 1

[000314] This example shows the preparation of the Cox-2 inhibitor, celecoxib.

[000315] Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione.

[000316] Following the disclosure provided in U.S. Patent No. 5,760,068, 4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 x 75 mL ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

[000317] Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

[000318] To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol, 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine hydrochloride was added. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid, having a melting point (mp) of 157°-159°C; and a calculated composition of C_{17} H_{14} N_3 O_2 SF_3 : C, 53.54; H, 3.70; N, 11.02. The composition that was found by analysis was: C, 53.17; H, 3.81; N, 10.90.

EXAMPLE 2

[000319] This illustrates the production of a composition containing the combination of celecoxib and a corticosteroid, and of a pharmaceutical composition containing the combination.

[000320] A therapeutic composition of the present invention can be formed by intermixing prednisone (10 g, available as Deltasone® in 10mg tablets from Pfizer, Inc., New York, NY) and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced

in Example 1, or available from Pfizer, Inc., New York, NY), in a laboratory mill or mixing device suitable for intimate mixing of powders without substantial generation of shear or temperature sufficient to degrade either of the two compounds. After mixing, the combination of celecoxib and prednisone form a therapeutic composition that is sufficient for the production of about 1000 single dose units. Each single dose unit contains about 10 mg of prednisone and about 200 mg of celecoxib.

[000321] If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for consumption, for example, by conventional capsule-forming equipment, where each capsule contains 10 mg of prednisone and 200 mg celecoxib.

[000322] Alternatively, the prednisone and the celecoxib may be dissolved into a liquid carrier, such as, for example, normal saline solution, to form a pharmaceutical composition suitable for human consumption. A single dosage of the liquid pharmaceutical composition for human use would be a volume sufficient to provide 10 mg of prednisone and 200 mg of celecoxib.

[000323] Therapeutic and pharmaceutical compositions comprising a combination of any of the Cox-2 inhibitors and any of the sources of corticosteroids that are described above can be formed by similar methods.

[000324] All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000325] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[000326] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense. In addition, it should be understood that aspects of the various embodiments may be interchanged both in whole or in part.